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(54) Title: HDAC9 POLYPEPTIDES AND POLYNUCLEOTIDES AND USES THEREOF

(57) Abstract: The present invention features substantially pure HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), an HDRP(Δ NLS) polypeptides, and isolated nucleic acid molecules encoding those polypeptides. The present invention also features vectors containing HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), and HDRP(Δ NLS) nucleic acid sequences, and cells containing those vectors.

HDAC9 POLYPEPTIDES AND POLYNUCLEOTIDES AND USES THEREOF

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No.

- 5 60/298,173 filed on June 14, 2001, U.S. Provisional Application No. 60/311,686
filed on August 10, 2001, and U.S. Provisional Application No. 60/316,995, filed on
September 4, 2001. The entire teachings of the above applications are incorporated
herein by reference.

10 GOVERNMENT SUPPORT

The invention was supported, in whole or in part, by grant CA-0974823 from
the National Cancer Institute. The Government has certain rights in the invention.

BACKGROUND OF THE INVENTION

- 15 The N-terminal tails of core histones are covalently modified by post-
translational modifications, including acetylation and phosphorylation. Evidence
suggests that these covalent modifications play important roles in several biological
activities involving chromatin, *e.g.*, transcription and replication. Histone
deacetylases (HDACs) catalyze the removal of the acetyl group from the lysine
20 residues in the N-terminal tails of nucleosomal core histones resulting in a more
compact chromatin structure, a configuration that is generally associated with
repression of transcription.

- Five proteins and/or open reading frames in yeast (RPD3, HDA1, HOS1,
HOS2 and HOS3) that share significant homology in the catalytic domain have been
25 identified as HDACs based upon their sequence homology to human HDAC1. To
date, eight HDACs have been identified in mammalian cells, and classified into two
classes based on their structure and similarity to yeast RPD3 or HDA1 proteins.
Recently, Sir2 family proteins that are structurally unrelated to the five proteins
aforementioned have been identified as NAD-dependent HDACs. Class I HDACs
30 are the yeast RPD3 homologs HDAC1, 2, 3, and 8, and are composed primarily of a
catalytic domain. Class II HDACs are the yeast HDA1 homologs HDAC4, 5, 6; and

7. HDAC4, 5, and 7 contain a long non-catalytic N-terminal end and a C-terminal HDAC catalytic domain while HDAC6 has two HDAC catalytic domains.

It has also been determined that histone deacetylases can be sensitive to small molecules, including trichostatin A (TSA), trapoxin, and butyrate. For example, the yeast RPD3 and HDA1 and mammalian HDAC1, 2, 3, 4, 5, 6, 7 and 8 are sensitive to inhibition by trichostatin A (TSA). The Sir2 family HDACs, yeast HOS3 and *Drosophila melanogaster* dHDAC6, however, appear to be relatively insensitive to TSA. A class of hybrid bipolar compounds, such as suberoylanilide hydroxamic acid (SAHA) have also been shown to inhibit histone deacetylases and induce terminal differentiation and/or apoptosis in various transformed cells. Examples of such compounds can be found in U.S. Patent Nos. 5,369,108, issued on November 29, 1994, 5,700,811, issued on December 23, 1997, and 5,773,474, issued on June 30, 1998 to Breslow *et al.*, as well as U.S. Patent Nos. 5,055,608, issued on October 8, 1991, and 5,175,191, issued on December 29, 1992 to Marks *et al.*, the entire content of all of which are hereby incorporated by reference.

The identification of the mechanisms by which histones are deacetylated, and the characterization of histone deacetylase function would be of great benefit in understanding how gene transcription is controlled, how the cell cycle is regulated, and how cells are signaled to undergo terminal differentiation and/or apoptosis. Elucidation of such mechanisms can lead to improved therapeutics for many diseases, in particular those characterized by cell proliferation or a lack of cell differentiation or apoptosis, for example, cancer.

SUMMARY OF THE INVENTION

The present invention relates to isolated or recombinant histone deacetylase polypeptides, and isolated histone deacetylase nucleic acid molecules encoding those polypeptides, as well as vectors and cells containing those isolated nucleic acid molecules.

In one aspect of the invention, the isolated or recombinant histone deacetylase polypeptide is selected from a) an isolated or recombinant polypeptide comprising SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10; and b) a polypeptide having at least 60% sequence identity with any one

of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10. In one embodiment, the isolated or recombinant histone deacetylase polypeptide consists of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10. In another embodiment, the isolated or recombinant histone deacetylase polypeptide is mammalian; preferably, the isolated or recombinant histone deacetylase polypeptide is human.

In another aspect, the invention features an isolated nucleic acid molecule selected from a) an isolated nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9; b) a complement of an isolated nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9; c) an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10; d) a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10; e) a nucleic acid that is hybridizable under high stringency conditions to a nucleic acid molecule that encodes any of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, or SEQ ID NO: 8, or a complement thereof; or f) a nucleic acid molecule that is hybridizable under high stringency conditions to a nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, or SEQ ID NO: 7; and g) an isolated nucleic acid molecule that has at least 55% sequence identity with any one of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, or a complement thereof. In one embodiment, the isolated nucleic acid molecule consists of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9. In another embodiment, the isolated nucleic acid molecule is mammalian; preferably, the isolated nucleic acid molecule is human.

In other aspects, the invention features a vector comprising the isolated histone deacetylase nucleic acid molecule described above, a cell comprising the vector, and a cell comprising the isolated histone deacetylase nucleic acid molecule described above.

In another aspect, the invention features a purified antibody that selectively binds a histone deacetylase polypeptide described above.

In yet another aspect, the invention features a method of identifying a compound that modulates expression of a histone deacetylase nucleic acid molecule described above. The method comprises the steps of a) contacting the nucleic acid molecule with a candidate compound under conditions suitable for expression; and
5 b) assessing the level of expression of the nucleic acid molecule. A candidate compound that increases or decreases expression of the nucleic acid molecule relative to a control is a compound that modulates expression of the nucleic acid molecule. In one embodiment, the method is carried out in a cell or animal. In another embodiment, the method is carried out in a cell free system.

10 The invention also features a method of treating a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, for example, cancers such as lymphoma, leukemia, melanoma, ovarian cancer, breast cancer, pancreatic cancer, prostate cancer, colon cancer, and lung cancer and myeloproliferative disorders, including polycythemia vera, essential thrombocythemia, agnogenic myeloid
15 metaplasia, and chronic myelogenous leukemia in an individual, comprising administering a compound identified by the above method.

In still another aspect, the invention features a method of identifying a compound that modulates the enzymatic activity of the histone deacetylase polypeptide described above. The method comprises the steps of a) contacting the
20 polypeptide with a candidate compound under conditions suitable for enzymatic reaction; and b) assessing the activity level of the polypeptide. A candidate compound that increases or decreases the activity level of the polypeptide relative to a control is a compound that modulates the enzymatic activity of the polypeptide. In one embodiment, the method is carried out in a cell or animal. In another
25 embodiment, the method is carried out in a cell free system.

In yet another embodiment, the polypeptide is further contacted with a substrate for the polypeptide, wherein the substrate is selected from the group consisting of a cell proliferation disease binding agent, an apoptotic disease binding agent, and a cell differentiation disease binding agent. In one embodiment, the
30 candidate compound is an inhibitor. In another embodiment, candidate compound is an activator.

In another aspect, the invention features a method of identifying a compound that modulates the transcriptional repression activity of the histone deacetylase polypeptide described above. The method comprises the steps of a) contacting the polypeptide with a candidate compound under conditions suitable for a
5 transcriptional repression reaction; and b) assessing the transcriptional repression activity level of the polypeptide. A candidate compound that increases or decreases the transcriptional repression activity level of the polypeptide relative to a control is a compound that modulates the transcriptional repression activity of the polypeptide. In one embodiment, the method is carried out in a cell or animal. In another
10 embodiment, the method is carried out in a cell free system.

In yet another embodiment, the polypeptide is further contacted with a substrate for the polypeptide, wherein the substrate is selected from the group consisting of a cell proliferation disease binding agent, an apoptotic disease binding agent, and a cell differentiation disease binding agent. In one embodiment, the
15 candidate compound is an inhibitor. In another embodiment, candidate compound is an activator.

In another aspect, the invention features a method of identifying a compound that modulates expression of a histone deacetylase nucleic acid molecule described above. The method comprises the steps of a) providing a nucleic acid molecule
20 comprising a promoter region of the histone deacetylase nucleic acid molecule described above, or part of such a promoter region, operably linked to a reporter gene; b) contacting the nucleic acid molecule or with a candidate compound; and c) assessing the level of the reporter gene. A candidate compound that increases or decreases expression of the reporter gene relative to a control is a compound that
25 modulates expression of the histone deacetylase nucleic acid molecule described above. In one embodiment, the method is carried out in a cell.

In still another aspect, the invention features a method of identifying a polypeptide that interacts with a histone deacetylase polypeptide described above in a yeast two-hybrid system. The method comprises the steps of a) providing a first
30 nucleic acid vector comprising a nucleic acid molecule encoding a DNA binding domain and the histone deacetylase polypeptide described above; b) providing a second nucleic acid vector comprising a nucleic acid encoding a transcription

activation domain and a nucleic acid encoding a test polypeptide; c) contacting the first nucleic acid vector with the second nucleic acid vector in a yeast two-hybrid system; and d) assessing transcriptional activation in the yeast two-hybrid system. An increase in transcriptional activation relative to a control indicates that the test
5 polypeptide is a polypeptide that interacts with the histone deacetylase polypeptide described above.

The invention also features a pharmaceutical composition comprising a histone deacetylase polypeptide described above.

In addition, the present invention features a method of diagnosing a cell
10 proliferation disease, an apoptotic disease, or a cell differentiation disease in a subject. The method comprises the steps of a) obtaining a sample from the subject; and b) assessing the level of activity or expression of the histone deacetylase polypeptide described above or the level of the nucleic acid molecule described above in the sample. If the level is increased relative to a control, then the subject
15 has an increased likelihood of having a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, and if the level is decreased relative to a control, then the subject has a decreased likelihood of having a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. In one embodiment, the polypeptide level is assayed using immunohistochemistry techniques. In another
20 embodiment, the nucleic acid molecule level is assayed using *in situ* hybridization techniques.

Compounds and/or polypeptides identified in the above-described screening methods are also part of the present invention.

25 DESCRIPTION OF THE FIGURES

FIG. 1 is a schematic representation of the order in which FIGS. 1A-1O should be viewed.

FIGS. 1A-1C show the cDNA sequence of *HDAC9* (SEQ ID NO: 1). The arrows and numbers in the *HDAC9* sequence indicate exons. The boxed portion of
30 the sequence indicates the HDAC domain.

FIGS. 1D-1G show the cDNA sequence of *HDAC9a* (SEQ ID NO: 3). The arrows and numbers in the *HDAC9a* sequence indicate exons. The boxed portion of the sequence indicates the HDAC domain.

FIGS. 1H-1I show the cDNA sequence of *HDRP*(Δ NLS) (SEQ ID NO:9).

5 FIGS. 1J-1L show the cDNA sequence of *HDAC9*(Δ NLS) (SEQ ID NO:5).

FIGS. 1M-1O show the cDNA sequence of *HDAC9a*(Δ NLS) (SEQ ID NO:7).

FIG. 2 is a schematic representation of the order in which FIGS. 2A-2E should be viewed.

10 FIG. 2A shows the amino acid sequence of HDAC9 (SEQ ID NO: 2).

FIG. 2B shows the amino acid sequence of HDAC9a (SEQ ID NO: 4).

FIG. 2C shows the amino acid sequence of HDAC9(Δ NLS) (SEQ ID NO: 6).

FIG. 2D shows the amino acid sequence of HDAC9a(Δ NLS) (SEQ ID NO: 8).

15 FIG. 2E shows the amino acid sequence of and HDRP(Δ NLS) (SEQ ID NO: 10).

FIG. 3 is a schematic representation of the order in which FIGS. 3A-3C should be viewed.

20 FIGS. 3A-3C show an amino acid sequence alignment of HDRP (SEQ ID NO: 11), HDAC9 (SEQ ID NO: 2), HDAC9a (SEQ ID NO: 4), and HDAC4 (SEQ ID NO: 12) polypeptides. Amino acid sequences of HDAC9 (GenBank Accession: AY032737; SEQ ID NO: 2) and HDAC9a (GenBank Accession: AY032738; SEQ ID NO: 4) are aligned with HDRP (GenBank Accession: BAA34464; SEQ ID NO: 11) and HDAC4 (GenBank Accession: NP_006028; SEQ ID NO: 12). The identical
25 residues in all proteins are boxed with solid lines. The similar residues are boxed with dotted lines.

FIG. 4 shows a schematic representation of the human *HDAC9* gene structure. The striped boxes represent exons present in isoforms HDRP, HDAC9a, and HDAC9. The lines represent introns. Broken lines are used for larger introns
30 (with size in base pair on top). The 5' untranslated region cDNA and coding region cDNA are represented here. Exons 1-12 encode a non-catalytic domain of the

polypeptides, and exons 14-21 encode the histone deacetylase catalytic domain of the polypeptides, which provide the polypeptides with deacetylase activity.

FIG. 5 is a schematic representation of the order in which FIGS. 5A-5D should be viewed.

5 FIGS. 5A-5D show the nucleic acid sequence of *HDAC9*, containing all exons expressed in the various isoforms of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* of the present invention (SEQ ID NO:13).

FIG. 6A is a scanned image of a multiple human tissue Northern blot that was probed to determine mRNA expression of *HDAC9* using a cDNA probe that
10 recognizes both *HDAC9* and *HDAC9a*. The tissues examined are lane 1, heart; lane 2, brain; lane 3, placenta; lane 4, lung; lane 5, liver; lane 6, skeletal muscle; lane 7, kidney; and lane 8, pancreas. Positions of the RNA size marker in kilobases (kb) are indicated to the left of the blot.

FIG. 6B is a scanned image of an electrophoretic gel showing the results of
15 RT-PCR analyses of mRNA from the same tissues as examined in the Northern blot of FIG. 6A to determine the distribution of *HDAC9* and *HDAC9a* mRNA among these tissues. PCR products were resolved by agarose gel electrophoresis and visualized by ethidium bromide under UV light. A 1-kb DNA ladder was run on both sides of the gel with the size (in kb) indicated on the left. On the right side, the
20 expected products for *HDAC9* and *HDAC9a* are indicated as 9 and 9a, respectively.

FIG. 7 is a graph of HDAC enzymatic activity of HDAC anti-FLAG-immunoprecipitated proteins isolated from vector control, HDAC9-FLAG, and HDAC9a-FLAG transfected 293T cells, as measured in fluorescence units using *FLUOR DE LYS*[™] as a substrate in the presence or absence of 1 μM TSA. Results
25 are shown as the mean of three independent assays. The inset is a scanned image of an anti-FLAG Western blot showing the amount of proteins used in the assay. V, Vector control; 9, HDAC9-FLAG; and 9a, HDAC9a-FLAG.

FIG. 8 is a graph of HDAC enzymatic activity of HDAC anti-FLAG-immunoprecipitated proteins isolated from vector control, and HDAC9a-FLAG
30 (treated with 2 μM SAHA or left untreated) transfected 293T cells, as measured by ³H-acetic acid released from ³H-histones in the presence or absence of 2 μM SAHA.

Vector control; HDAC9a, HDAC9a-FLAG; and HDAC9a+, HDAC9a-FLAG + SAHA.

FIG. 9A shows a scanned image of a Western blot of 293T whole cell lysate and anti-FLAG immunoprecipitates from 293T cells transfected with vector,

5 HDAC9-FLAG or HDAC9a-FLAG using antibodies against MEF2 and FLAG. Top panel, anti-MEF2 Western; bottom panel, anti-FLAG Western. L, 293T whole cell lysate; V, vector control IP; 9, HDAC9-FLAG IP; 9a, HDAC9a-FLAG IP.

FIG. 9B is a graph showing the transcription level of p3XMEF2-*Luc* in the presence or absence of pcDNA3 empty vector (-), pCMV-MEF2C, and/or a vector
10 encoding pFLAG-HDAC9 or pFLAG-HDAC9a. p3XMEF2-*Luc* (100 ng) and pRL-TK (5 ng) were transfected into 293T cells with pcDNA3 empty vector (-) or with pCMV-MEF2C (100 ng) (+) along with the indicated amount of pFLAG-HDAC9 or pFLAG-HDAC9a. pFLAG empty vector was used to adjust the DNA to an equal amount in each transfection. The firefly luciferase activity was first normalized to
15 the co-transfected Renilla luciferase activity and the value for MEF2C alone was then set as 1. Results are shown as the mean of three independent transfections +/- standard deviation.

FIG. 10 shows a schematic representation of the HDAC domains of human non-Sir2 family HDACs and HDRP. The boxes represent histone deacetylase
20 (HDAC) domains.

FIG. 11 is a schematic representation of the order in which FIGS. 11A-11F should be viewed.

FIGS. 11A-11F show the nucleotide sequence of the vector pFLAG-CMV-5b-HDAC9 (VR1) (SEQ ID NO: 14). Lowercase letters are vector backbone,
25 uppercase letters are HDAC9 sequence. "Acc" was added at the beginning of the HDAC9 sequence for translation initiation.

FIG. 12 is a schematic representation of the order in which FIGS. 12-1 through 12-66 should be viewed.

FIGS. 12-1 through 12-66 show the nucleotide sequence of the vector
30 pFLAG-CMV-5b-HDAC9a (VR2), with restriction enzyme sites indicated (SEQ ID NO: 14).

FIG. 13 is a schematic representation of the order in which FIGS. 13A-13E should be viewed.

FIGS. 13A-13E show the nucleotide sequence of the vector pFLAG-CMV-5b-HDAC9a (VR2) (SEQ ID NO: 15). Lowercase letters are vector backbone, 5 uppercase letters are HDAC9a sequence. "Acc" was added at the beginning of the HDAC9a sequence for translation initiation.

FIG. 14 is a schematic representation of the order in which FIGS. 14-1 through 14-61 should be viewed.

FIGS. 14-1 through 14-61 show the nucleotide sequence of the vector 10 pFLAG-CMV-5b-HDAC9a (VR2), with restriction enzyme sites indicated (SEQ ID NO: 15).

DETAILED DESCRIPTION OF THE INVENTION

A protein designated HDRP (See Zhou *et al.*, Proc. Natl. Acad. Sci. USA, 15 97:1056-1061 (2000)) (also called MITR (See Sparrow *et al.*, EMBO J. 18:5085-5098(1999); Zhang *et al.*, J. Biol. Chem., 276:35-39 (2001); and Zhang *et al.*, Proc. Natl. Acad. Sci. USA, 98:7354-7359 (2001)) that is 50% identical to the N-terminal domains of histone deacetylase 4 (HDAC4) and histone deacetylase 5 (HDAC5) was recently identified. The cloning and characterization of a novel histone deacetylase, 20 *HDAC9*, of which HDRP is an alternatively spliced isoform is described herein. The cDNA sequence of *HDAC9* is shown in FIGS. 1A-1C (SEQ ID NO: 1), and the HDAC9 amino acid sequence is shown in FIG. 2A (SEQ ID NO: 2). In addition to cloning *HDAC9*, other alternatively spliced isoforms of HDAC9, designated as HDAC9a (a polypeptide that is 132 amino acids shorter at the C-terminal end than 25 HDAC9), and isoforms of HDAC9, HDAC9a, and HDRP polypeptides that lack the nuclear localization signal (NLS) in the N-terminal non-catalytic end of HDAC9, termed HDAC9(Δ NLS), HDAC9a(Δ NLS), and HDRP(Δ NLS), respectively were also identified. The cDNA sequence of *HDAC9a* is shown in FIGS. 1D-1G (SEQ ID NO: 3), and the HDAC9a amino acid sequence is shown in FIG. 2B (SEQ ID 30 NO: 4). The cDNA sequence of *HDAC9* lacking amino acids encoding an NLS (*HDAC9*(Δ NLS)) is shown in FIGS. 1J-1L (SEQ ID NO: 5), and the HDAC9 lacking an NLS amino acid sequence is shown in FIG. 2C (SEQ ID NO: 6). The cDNA

sequence of *HDAC9a* encoding a polypeptide lacking an NLS (*HDAC9a(ΔNLS)*) is shown in FIGS. 1M-1O (SEQ ID NO: 7), and the *HDAC9a* lacking an NLS amino acid sequence is shown in FIG. 2D (SEQ ID NO: 8). The cDNA sequence of *HDRP* encoding a polypeptide lacking an NLS (*HDRP(ΔNLS)*) is shown in FIGS. 1H-1I (SEQ ID NO: 9), and the *HDRP* lacking an NLS amino acid sequence is shown in FIG. 2E (SEQ ID NO: 10).

POLYPEPTIDES OF THE INVENTION

The present invention features isolated or recombinant *HDAC9* polypeptides, *HDAC9a* polypeptides, *HDAC9(ΔNLS)* polypeptides, *HDAC9a(ΔNLS)* polypeptides, and *HDRP(ΔNLS)* polypeptides, and fragments, derivatives, and variants thereof, as well as polypeptides encoded by nucleotide sequences described herein (e.g., other variants). As used herein, the term “polypeptide” refers to a polymer of amino acids, and not to a specific length; thus, peptides, oligopeptides, and proteins are included within the definition of a polypeptide.

As used herein, a polypeptide is said to be “isolated,” “substantially pure,” or “substantially pure and isolated” when it is substantially free of cellular material, when it is isolated from recombinant or non-recombinant cells, or free of chemical precursors or other chemicals when it is chemically synthesized. Typically, the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide is isolated, substantially pure, or substantially pure and isolated when it has a relative increased concentration or activity of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, in comparison to total *HDAC* concentration or activity. Preferably the increased activity or concentration of the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* is at least 2-fold, more preferably, at least 5-fold, and most preferably, at least 10 fold, in comparison to total *HDAC* concentration or activity. In addition, a polypeptide can be joined to another polypeptide with which it is not normally associated in a cell (e.g., in a “fusion protein”) and still be “isolated,” “substantially pure,” or “substantially pure and isolated.” An isolated, substantially pure, or substantially pure and isolated polypeptide may be obtained, for example, using affinity

purification techniques described herein, as well as other techniques described herein and known to those skilled in the art.

By a "histone deacetylase polypeptide" is meant a polypeptide having histone deacetylase activity, transcription repression activity, and/or the ability to deacetylate other substrates, for example, transcription factors, including p53, CoRest, E2F, GATA-1, TFIIe, and TFIIIF that normally have a nuclear or cytoplasmic location in a cell. A histone deacetylase polypeptide is also a polypeptide whose activity can be inhibited by molecules having HDAC inhibitory activity. These molecules fall into four general classes: 1) short-chain fatty acids (e.g., 4-phenylbutyrate and valproic acid); 2) hydroxamic acids(e.g. SAHA, Pyroxamide, trichostatin A (TSA), oxamflatin and CHAPs, such as, CHAP1 and CHAP 31); 3) cyclic tetrapeptides (Trapoxin A, Apicidin and Depsipeptide (FK-228, also known as FR9011228); 4) benzamides (e.g., MS-275); and other compounds such as Scriptaid. Examples of such compounds can be found in U.S. Patent Nos. 5,369,108, issued on November 29, 1994, 5,700,811, issued on December 23, 1997, and 5,773,474, issued on June 30, 1998 to Breslow *et al.*, U.S. Patent Nos. 5,055,608, issued on October 8, 1991, and 5,175,191, issued on December 29, 1992 to Marks *et al.*, as well as, Yoshida *et al.*, Bioessays 17, 423-430 (1995), Saito *et al.*, PNAS USA 96, 4592-4597, (1999), Furumai *et al.*, PNAS USA 98 (1), 87-92 (2001), Komatsu *et al.*, Cancer Res. 61(11), 4459-4466 (2001), Su *et al.*, Cancer Res. 60, 3137-3142 (2000), Lee *et al.*, Cancer Res. 61(3), 931-934 and Suzuki *et al.* J. Med. Chem. 42(15), 3001-3003 (1999) the entire content of all of which are hereby incorporated by reference. Examples of such histone deacetylase polypeptides include HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), HDRP(Δ NLS); a substantially pure polypeptide comprising SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10; and a polypeptide having preferably at least 60%, more preferably, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% sequence identity to any one of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10, as determined using the BLAST program and parameters described herein.

In one embodiment, the histone deacetylase polypeptide has histone deacetylase activity, transcription repression activity, the ability to deacetylate substrates, or is inhibited by trichostatin A or a hybrid polar compound such as

SAHA. In another embodiment, the HDAC9(Δ NLS) polypeptide has any two of the above biological activities. In still another embodiment, the HDAC9(Δ NLS) polypeptide has any three of the above biological activities. In yet another embodiment, the HDAC9(Δ NLS) polypeptide has all of the above biological activities.

- 5 An HDAC9 polypeptide is a histone deacetylase polypeptide as described above. An HDAC9 polypeptide preferably has at least 60%, more preferably, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% sequence identity to SEQ ID NO: 2, as determined using the BLAST program and parameters described herein.
- 10 An HDAC9 polypeptide is also a polypeptide that comprises the amino acids encoded by exons 23, 24, 25 and/or 26, and that does not comprise the amino acids encoded by exon 13 of the *HDAC9* nucleic acid sequence, as shown in FIGS. 1A-1C, FIG. 4, and FIGS. 5A-5D. Preferably, an HDAC9 polypeptide comprises the sequence of SEQ ID NO: 2. More preferably, an HDAC9 polypeptide consists of
- 15 the sequence of SEQ ID NO: 2. An HDAC polypeptide is also a polypeptide comprising the amino acid sequence of the polypeptide encoded by the nucleic acid sequence of SEQ ID NO: 1.

- An HDAC9a polypeptide is a histone deacetylase polypeptide as described above. An HDAC9a polypeptide preferably has at least 60%, more preferably, 70%,
- 20 75%, 80%, 85%, or 90%, and most preferably, 95% sequence identity to SEQ ID NO: 4, as determined using the BLAST program and parameters described herein. An HDAC9a polypeptide is also a polypeptide that comprises the amino acids encoded by exon 22, and that does not comprise the amino acids encoded by exons 13, 23, 24, 25, or 26 of the *HDAC9* nucleic acid sequence, as shown in FIGS. 1D-
- 25 1G, FIG. 4, and FIGS. 5A-5D. Preferably, an HDAC9a polypeptide comprises the sequence of SEQ ID NO: 4. More preferably, an HDAC9a polypeptide consists of the sequence of SEQ ID NO: 4. An HDAC9a polypeptide is also a polypeptide comprising the amino acid sequence of the polypeptide encoded by the nucleic acid sequence of SEQ ID NO: 3.

- 30 An HDAC9(Δ NLS) is a histone deacetylase polypeptide as described above. An HDAC9(Δ NLS) polypeptide does not comprise a nuclear localization signal (NLS). An HDAC9(Δ NLS) polypeptide preferably has at least 60%, more

preferably, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% sequence identity to SEQ ID NO: 6, as determined using the BLAST program and parameters described herein. An HDAC9(Δ NLS) polypeptide is also a polypeptide that comprises the amino acids encoded by exons 23, 24, 25, and/or 26, and that does not
5 comprise the amino acids encoded by exons 7 or 13 of the *HDAC9* nucleic acid sequence, as shown in FIGS. 1J-1L, and FIGS. 5A-5D. Preferably, an HDAC9(Δ NLS) polypeptide comprises the sequence of SEQ ID NO: 6. More preferably, an HDAC9(Δ NLS) polypeptide consists of the sequence of SEQ ID NO: 6. An HDAC9(Δ NLS) polypeptide is also a polypeptide comprising the amino acid
10 sequence of the polypeptide encoded by the nucleic acid sequence of SEQ ID NO: 5.

An HDAC9a(Δ NLS) polypeptide is a histone deacetylase polypeptide as described above. An HDAC9a(Δ NLS) does not comprise a nuclear localization signal (NLS). An HDAC9a(Δ NLS) polypeptide preferably has at least 60%, more preferably, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% sequence
15 identity to SEQ ID NO: 8, as determined using the BLAST program and parameters described herein. An HDAC9a(Δ NLS) polypeptide is also a polypeptide that comprises the amino acids encoded by exon 22, and that does not comprise the amino acids encoded by exons 7, 13, 23, 24, 25, or 26 of the *HDAC9* nucleic acid sequence, as shown in FIGS. 1M-1O, and FIGS. 5A-5D. Preferably, an
20 HDAC9a(Δ NLS) polypeptide comprises the sequence of SEQ ID NO: 8. More preferably, an HDAC9a(Δ NLS) polypeptide consists of the sequence of SEQ ID NO: 8. An HDAC9a(Δ NLS) polypeptide is also a polypeptide comprising the amino acid sequence of the polypeptide encoded by the nucleic acid sequence of SEQ ID NO: 7.

An HDRP(Δ NLS) polypeptide is a histone deacetylase polypeptide as
25 described above. An HDRP(Δ NLS) does not comprise a nuclear localization signal (NLS). An HDRP(Δ NLS) polypeptide preferably has at least 60%, more preferably, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% sequence identity to SEQ ID NO: 10, as determined using the BLAST program and parameters described herein. An HDRP(Δ NLS) polypeptide is also a polypeptide that does not comprise
30 the amino acids encoded by exons 7 or 13-26 of the *HDAC9* nucleic acid sequence, as shown in FIGS. 1H-1I and FIGS. 5A-5D. Preferably, an HDRP(Δ NLS) polypeptide comprises the sequence of SEQ ID NO: 10. More preferably, an

HDRP(Δ NLS) polypeptide consists of the sequence of SEQ ID NO: 10. An HDRP(Δ NLS) polypeptide is also a polypeptide comprising the amino acid sequence of the polypeptide encoded by the nucleic acid sequence of SEQ ID NO: 9.

The polypeptides of the invention can be purified to homogeneity. It is understood, however, that preparations in which the polypeptide is not purified to homogeneity are useful. The critical feature is that the preparation allows for the desired function of the polypeptide, even in the presence of considerable amounts of other components. Thus, the invention encompasses various degrees of purity. In one embodiment, the language "substantially free of cellular material" includes preparations of the polypeptide having less than about 30% (by dry weight) other proteins (*i.e.*, contaminating protein), less than about 20% other proteins, less than about 10% other proteins, or less than about 5% other proteins.

When a polypeptide is recombinantly produced, it can also be substantially free of culture medium, *i.e.*, culture medium represents less than about 20%, less than about 10%, or less than about 5% of the volume of the polypeptide preparation. The language "substantially free of chemical precursors or other chemicals" includes preparations of the polypeptide in which it is separated from chemical precursors or other chemicals that are involved in its synthesis. In one embodiment, the language "substantially free of chemical precursors or other chemicals" includes preparations of the polypeptide having less than about 30% (by dry weight) chemical precursors or other chemicals, less than about 20% chemical precursors or other chemicals, less than about 10% chemical precursors or other chemicals, or less than about 5% chemical precursors or other chemicals.

In one embodiment, a polypeptide of the invention comprises an amino acid sequence encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, and complements and portions thereof, (*e.g.*, a complement of any one of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9 or a portion of any one of SEQ ID NO: 1 or SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9).

The polypeptides of the invention also encompass fragments and sequence variants. Variants include a substantially homologous polypeptide encoded by the

- same genetic locus in an organism, *i.e.*, an allelic variant, as well as other variants. Variants also encompass polypeptides derived from other genetic loci in an organism, but having substantial homology to a polypeptide encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, and complements and portions thereof, or having substantial homology to a polypeptide encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of nucleotide sequences encoding any one of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10.
- 10 Variants also include polypeptides substantially homologous or identical to these polypeptides but derived from another organism, *i.e.*, an ortholog. Variants also include polypeptides that are substantially homologous or identical to these polypeptides that are produced by chemical synthesis. Variants also include polypeptides that are substantially homologous or identical to these polypeptides that are produced by recombinant methods.
- 15

- As used herein, two polypeptides (or a region of the polypeptides) are substantially homologous or identical when the amino acid sequences are at least about 60-65%, typically at least about 70-75%, more typically at least about 80-85%, and most typically greater than about 90-95% or more homologous or identical. A substantially identical or homologous amino acid sequence, according to the present invention, will be encoded by a nucleic acid molecule hybridizing to SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, or a portion thereof, under stringent conditions as more particularly described herein, or will be encoded by a nucleic acid molecule hybridizing to a nucleic acid sequence encoding SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, or portion thereof, under stringent conditions as more particularly described herein.
- 20
- 25

- The percent identity of two nucleotide or amino acid sequences can be determined by aligning the sequences for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first sequence). The nucleotides or amino acids at corresponding positions are then compared, and the percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % identity = # of identical positions/total # of positions x 100). In
- 30

certain embodiments, the length of the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), and HDRP(Δ NLS) amino acid or nucleotide sequence aligned for comparison purposes is at least 30%, preferably, at least 40%, more preferably, at least 60%, and even more preferably, at least 70%, 80%, 90%, or 100% of the length of the reference sequence, for example, those sequences provided in FIGS. 1A-1O and 2A-2E. The actual comparison of the two sequences can be accomplished by well-known methods, for example, using a mathematical algorithm. A preferred, non-limiting example of such a mathematical algorithm is described in Karlin *et al.*, Proc. Natl. Acad. Sci. USA, 90:5873-5877 (1993). Such an algorithm is incorporated into the BLASTN and BLASTX programs (version 2.2) as described in Schaffer *et al.*, Nucleic Acids Res., 29:2994-3005 (2001). When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, BLASTN) can be used. See <http://www.ncbi.nlm.nih.gov>, as available on August 10, 2001. In one embodiment, the database searched is a non-redundant (NR) database, and parameters for sequence comparison can be set at: no filters; Expect value of 10; Word Size of 3; the Matrix is BLOSUM62; and Gap Costs have an Existence of 11 and an Extension of 1.

Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, CABIOS (1989). Such an algorithm is incorporated into the ALIGN program (version 2.0), which is part of the GCG (Accelrys) sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. Additional algorithms for sequence analysis are known in the art and include ADVANCE and ADAM as described in Torellis and Robotti, Comput. Appl. Biosci., 10: 3-5 (1994); and FASTA described in Pearson and Lipman, Proc. Natl. Acad. Sci USA, 85: 2444-8 (1988).

In another embodiment, the percent identity between two amino acid sequences can be accomplished using the GAP program in the GCG software package (available at <http://www.accelrys.com>, as available on August 31, 2001) using either a Blossom 63 matrix or a PAM250 matrix, and a gap weight of 12, 10, 8, 6, or 4 and a length weight of 2, 3, or 4. In yet another embodiment, the percent

identity between two nucleic acid sequences can be accomplished using the GAP program in the GCG software package (available at <http://www.cgc.com>), using a gap weight of 50 and a length weight of 3.

- The invention also encompasses HDAC9, HDAC9a, HDAC9(Δ NLS),
- 5 HDAC9a Δ NLS, and HDRP(Δ NLS) polypeptides having a lower degree of identity but having sufficient similarity so as to perform one or more of the same functions performed by an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a Δ NLS, or HDRP(Δ NLS) polypeptide encoded by a nucleic acid molecule of the invention. Similarity is determined by conserved amino acid substitution. Such substitutions
- 10 are those that substitute a given amino acid in a polypeptide by another amino acid of like characteristics. Conservative substitutions are likely to be phenotypically silent. Typically seen as conservative substitutions are the replacements, one for another, among the aliphatic amino acids Ala, Val, Leu, and Ile; interchange of the hydroxyl residues Ser and Thr; exchange of the acidic residues Asp and Glu;
- 15 substitution between the amide residues Asn and Gln; exchange of the basic residues Lys and Arg; and replacements among the aromatic residues Phe and Tyr. Guidance concerning which amino acid changes are likely to be phenotypically silent are found in Bowie *et al.*, Science 247: 1306-1310 (1990).

- A variant polypeptide can differ in amino acid sequence by one or more
- 20 substitutions, deletions, insertions, inversions, fusions, and truncations or a combination of any of these. Further, variant polypeptides can be fully functional or can lack function in one or more activities, for example, in histone deacetylase activity or transcription repression activity. Fully functional variants typically contain only conservative variation or variation in non-critical residues or in
- 25 non-critical regions. Functional variants can also contain substitution of similar amino acids that result in no change or an insignificant change in function. Alternatively, such substitutions may positively or negatively affect function to some degree. Non-functional variants typically contain one or more non-conservative amino acid substitutions, deletions, insertions, inversions, or truncations or a
- 30 substitution, insertion, inversion, or deletion in a critical residue or critical region, such critical regions include the HDAC domains, which provide the polypeptide

with deacetylase activity, as shown in the nucleic acid sequences of FIGS. 1A-1G, as well as in the schematic of FIG. 4.

Amino acids that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham *et al.*, Science, 244: 1081-1085 (1989)). The latter procedure introduces a single alanine mutation at each of the residues in the molecule (one mutation per molecule). The resulting mutant molecules are then tested for biological activity *in vitro*. Sites that are critical for polypeptide activity can also be determined by structural analysis, such as crystallization, nuclear magnetic resonance, or photoaffinity labeling (See Smith *et al.*, J. Mol. Biol., 224: 899-904 (1992); and de Vos *et al.* Science, 255: 306-312 (1992)).

The invention also includes HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), and HDRP(Δ NLS) polypeptide fragments of the polypeptides of the invention. Fragments can be derived from a polypeptide comprising SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10, or from a polypeptide encoded by a nucleic acid molecule comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9 or a portion thereof and the complements thereof or other variants. The present invention also encompasses fragments of the variants of the polypeptides described herein. Useful fragments include those that retain one or more of the biological activities of the polypeptide as well as fragments that can be used as an immunogen to generate polypeptide-specific antibodies.

Biologically active fragments (peptides that are, for example, 6, 9, 12, 15, 16, 20, 30, 35, 36, 37, 38, 39, 40, 50, 100, or more amino acids in length) can comprise a domain, segment, or motif, for example, an HDAC domain, that has been identified by analysis of the polypeptide sequence using well-known methods, *e.g.*, signal peptides, extracellular domains, one or more transmembrane segments or loops, ligand binding regions, zinc finger domains, DNA binding domains, acylation sites, glycosylation sites, or phosphorylation sites.

Fragments can be discrete (not fused to other amino acids or polypeptides) or can be within a larger polypeptide. Further, several fragments can be comprised within a single larger polypeptide. In one embodiment a fragment designed for

expression in a host can have heterologous pre- and pro-polypeptide regions fused to the amino terminus of the polypeptide fragment and an additional region fused to the carboxyl terminus of the fragment.

The invention thus provides chimeric or fusion polypeptides. These
5 comprise an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a Δ NLS, or HDRP(Δ NLS) polypeptide of the invention operatively linked to a heterologous protein or polypeptide having an amino acid sequence not substantially homologous to the polypeptide. "Operatively linked" indicates that the polypeptide and the heterologous protein are fused in-frame. The heterologous protein can be fused to
10 the N-terminus or C-terminus of the polypeptide. In one embodiment, the fusion polypeptide does not affect the function of the polypeptide per se. For example, the fusion polypeptide can be a GST-fusion polypeptide in which the polypeptide sequences are fused to the C-terminus of the GST sequences. Other types of fusion polypeptides include, but are not limited to, enzymatic fusion polypeptides, for
15 example, β -galactosidase fusions, yeast two-hybrid GAL fusions, poly-His fusions, and Ig fusions. Such fusion polypeptides, particularly poly-His fusions, can facilitate the purification of recombinant polypeptide. In certain host cells (*e.g.*, mammalian host cells), expression and/or secretion of a polypeptide can be increased by using a heterologous signal sequence. Therefore, in another
20 embodiment, the fusion polypeptide contains a heterologous signal sequence at its N-terminus.

EP-A 0464 533 discloses fusion proteins comprising various portions of immunoglobulin constant regions. The Fc is useful in therapy and diagnosis and thus results, for example, in improved pharmacokinetic properties (EP-A 0232 262).
25 In drug discovery, for example, human proteins have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists. (See Bennett *et al.*, Journal of Molecular Recognition, 8: 52-58 (1995) and Johanson *et al.*, The Journal of Biological Chemistry, 270,16: 9459-9471 (1995)). Thus, this invention also encompasses soluble fusion polypeptides containing a polypeptide of
30 the invention and various portions of the constant regions of heavy or light chains of immunoglobulins of various subclass (IgG, IgM, IgA, IgE).

- A chimeric or fusion polypeptide can be produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different polypeptide sequences are ligated together in-frame in accordance with conventional techniques. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of nucleic acid fragments can be carried out using anchor primers that give rise to complementary overhangs between two consecutive nucleic acid fragments that can subsequently be annealed and re-amplified to generate a chimeric nucleic acid sequence (see Ausubel *et al.*, "Current Protocols in Molecular Biology," John Wiley & Sons, (1998), the entire teachings of which are incorporated by reference herein). Moreover, many expression vectors are commercially available that already encode a fusion moiety (*e.g.*, a GST protein). A nucleic acid molecule encoding a polypeptide of the invention can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the polypeptide.
- 15 The substantially pure, isolated, or substantially pure and isolated HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a Δ NLS, or HDRP(Δ NLS) polypeptide can be purified from cells that naturally express it, purified from cells that have been altered to express it (recombinant), or synthesized using known protein synthesis methods. In one embodiment, the polypeptide is produced by recombinant DNA techniques.
- 20 For example, a nucleic acid molecule encoding the polypeptide is cloned into an expression vector, the expression vector introduced into a host cell, and the polypeptide expressed in the host cell. The polypeptide can then be isolated from the cells by an appropriate purification scheme using standard protein purification techniques.
- 25 In general, HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a Δ NLS, and HDRP(Δ NLS) polypeptides of the present invention can be used as a molecular weight marker on SDS-PAGE gels or on molecular sieve gel filtration columns using art-recognized methods. The polypeptides of the present invention can be used to raise antibodies or to elicit an immune response. The polypeptides can also
- 30 be used as a reagent, *e.g.*, a labeled reagent, in assays to quantitatively determine levels of the polypeptide or a molecule to which it binds (*e.g.*, a receptor or a ligand) in biological fluids. The polypeptides can also be used as markers for cells or tissues

in which the corresponding polypeptide is preferentially expressed, either constitutively, during tissue differentiation, or in a diseased state. The polypeptides can be used to isolate a corresponding binding agent, and to screen for peptide or small molecule antagonists or agonists of the binding interaction. The polypeptides
5 of the present invention can also be used as therapeutic agents.

NUCLEIC ACID MOLECULES OF THE INVENTION

The present invention also features isolated *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleic acid molecules.

10 By a "histone deacetylase nucleic acid molecule" is meant a nucleic acid molecule that encodes a histone deacetylase polypeptide. Such histone nucleic acids include, for example, the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule described in detail herein; an isolated nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or
15 SEQ ID NO: 9; a complement of an isolated nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9; an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10; a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2,
20 SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10; a nucleic acid that is hybridizable under high stringency conditions to a nucleic acid molecule that encodes any of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, or SEQ ID NO: 8, or a complement thereof; a nucleic acid molecule that is hybridizable under high stringency conditions to a nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3,
25 SEQ ID NO: 5, or SEQ ID NO: 7; and an isolated nucleic acid molecule that has at least 55%, more preferably, 60%, 65%, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% or 99% sequence identity with any one of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, or a complement thereof.

An *HDAC9* nucleic acid molecule is a nucleic acid molecule that encodes an
30 *HDAC9* polypeptide. In one embodiment, the *HDAC9* nucleic acid molecule is selected from: a nucleic acid molecule that comprises the nucleic acid sequence of SEQ ID NO: 1; a complement of an isolated nucleic acid comprising SEQ ID NO: 1;

an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2; a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2; a nucleic acid that is hybridizable under high stringency conditions to a nucleic acid molecule that encodes SEQ ID NO: 2; a nucleic acid molecule that is hybridizable under high stringency conditions to a nucleic acid comprising SEQ ID NO: 1; and an isolated nucleic acid molecule that has preferably, at least 55%, more preferably, 60%, 65%, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% or 99% sequence identity with SEQ ID NO: 1, as determined using the BLAST program and parameters described herein. In another embodiment, the *HDAC9* nucleic acid molecule consists of the nucleic acid sequence of SEQ ID NO: 1.

An *HDAC9a* nucleic acid molecule is a nucleic acid molecule that encodes an *HDAC9a* polypeptide. An *HDAC9a* nucleic acid molecule preferably has at least 55%, sequence identity to SEQ ID NO: 3. In one embodiment, the *HDAC9a* nucleic acid molecule is selected from: a nucleic acid molecule that comprises the nucleic acid sequence of SEQ ID NO: 3; a complement of an isolated nucleic acid comprising SEQ ID NO: 3; an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 4; a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 4; a nucleic acid that is hybridizable under high stringency conditions to a nucleic acid molecule that encodes SEQ ID NO: 4; a nucleic acid molecule that is hybridizable under high stringency conditions to a nucleic acid comprising SEQ ID NO: 3; and an isolated nucleic acid molecule that has preferably, at least 55%, more preferably, 60%, 65%, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% or 99% sequence identity with SEQ ID NO: 3 or a complement thereof, as determined using the BLAST program and parameters described herein. In another embodiment, the *HDAC9a* nucleic acid molecule consists of the nucleic acid sequence of SEQ ID NO: 3.

An *HDAC9(ΔNLS)* nucleic acid molecule is a nucleic acid molecule that encodes an *HDAC9(ΔNLS)* polypeptide. In one embodiment, the *HDAC9(ΔNLS)* nucleic acid molecule is selected from: a nucleic acid molecule that comprises the nucleic acid sequence of SEQ ID NO: 5; a complement of an isolated nucleic acid comprising SEQ ID NO: 5; an isolated nucleic acid encoding a histone deacetylase

polypeptide of SEQ ID NO: 6; a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 6; a nucleic acid that is hybridizeable under high stringency conditions to a nucleic acid molecule that encodes SEQ ID NO: 6; a nucleic acid molecule that is hybridizeable under high stringency conditions to a nucleic acid comprising SEQ ID NO: 5; and an isolated nucleic acid molecule that has preferably, at least 55%, more preferably, 60%, 65%, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% or 99% sequence identity with SEQ ID NO: 5 or a complement thereof, as determined using the BLAST program and parameters described herein. In another embodiment, the

10 *HDAC9a(ΔNLS)* nucleic acid molecule consists of the nucleic acid sequence of SEQ ID NO: 5.

An *HDAC9a(ΔNLS)* nucleic acid molecule is a nucleic acid molecule that encodes an *HDAC9a(ΔNLS)* polypeptide. In one embodiment, the *HDAC9a(ΔNLS)* nucleic acid molecule is selected from: a nucleic acid molecule that comprises the

15 nucleic acid sequence of SEQ ID NO: 7; a complement of an isolated nucleic acid comprising SEQ ID NO: 7; an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 8; a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 8; a nucleic acid that is hybridizeable under high stringency conditions to a nucleic acid molecule that

20 encodes SEQ ID NO: 8; a nucleic acid molecule that is hybridizeable under high stringency conditions to a nucleic acid comprising SEQ ID NO: 7; and an isolated nucleic acid molecule that has preferably, at least 55%, more preferably, 60%, 65%, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% or 99% sequence identity with SEQ ID NO: 7 or a complement thereof, as determined using the BLAST

25 program and parameters described herein. In another embodiment, the *HDAC9a(ΔNLS)* nucleic acid molecule consists of the nucleic acid sequence of SEQ ID NO: 7.

An "*HDRP(ΔNLS)* nucleic acid molecule" is a nucleic acid molecule that encodes an *HDRP(ΔNLS)* polypeptide. In one embodiment, the *HDRP(ΔNLS)*

30 nucleic acid molecule is selected from: a nucleic acid molecule that comprises the nucleic acid sequence of SEQ ID NO: 9; a complement of an isolated nucleic acid comprising SEQ ID NO: 9; an isolated nucleic acid encoding a histone deacetylase

polypeptide of SEQ ID NO: 10; a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 10; and an isolated nucleic acid molecule that has preferably, at least 55%, more preferably, 60%, 65%, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% or 99% sequence identity with SEQ ID NO: 9 or a complement thereof, as determined using the BLAST program and parameters described herein.. In another embodiment, the *HDRP(ΔNLS)* nucleic acid molecule consists of the nucleic acid sequence of SEQ ID NO: 9.

The isolated nucleic acid molecules of the present invention can be RNA, for example, mRNA, or DNA, such as cDNA and genomic DNA. DNA molecules can be double-stranded or single-stranded; single stranded RNA or DNA can be either the coding, or sense, strand or the non-coding, or antisense, strand. The nucleic acid molecule can include all or a portion of the coding sequence of the gene and can further comprise additional non-coding sequences such as introns and non-coding 3' and 5' sequences (including regulatory sequences, for example). Additionally, the nucleic acid molecule can be fused to a marker sequence, for example, a sequence that encodes a polypeptide to assist in isolation or purification of the polypeptide. Such sequences include, but are not limited to, those that encode a glutathione-S-transferase (GST) fusion protein and those that encode a hemagglutinin A (HA) polypeptide marker from influenza.

An "isolated," "substantially pure," or "substantially pure and isolated" nucleic acid molecule, as used herein, is one that is separated from nucleic acids that normally flank the gene or nucleotide sequence (as in genomic sequences) and/or has been completely or partially purified from other transcribed sequences (*e.g.*, as in an RNA or cDNA library). For example, an isolated nucleic acid of the invention may be substantially isolated with respect to the complex cellular milieu in which it naturally occurs, or culture medium when produced by recombinant techniques, or chemical precursors or other chemicals when chemically synthesized. In some instances, the isolated material will form part of a composition (for example, a crude extract containing other substances), buffer system, or reagent mix. In other circumstances, the material may be purified to essential homogeneity, for example, as determined by agarose gel electrophoresis or column chromatography such as

HPLC. Preferably, an isolated nucleic acid molecule comprises at least about 50, 80, or 90% (on a molar basis) of all macromolecular species present.

With regard to genomic DNA, the term "isolated" also can refer to nucleic acid molecules that are separated from the chromosome with which the genomic DNA is naturally associated. For example, the isolated nucleic acid molecule can contain less than about 5 kb, 4 kb, 3 kb, 2 kb, 1 kb, 0.5 kb, or 0.1 kb of nucleotides that flank the nucleic acid molecule in the genomic DNA of the cell from which the nucleic acid molecule is derived.

The *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule can be fused to other coding or regulatory sequences and still be considered isolated. Thus, recombinant DNA contained in a vector is included in the definition of "isolated" as used herein. Also, isolated nucleic acid molecules include recombinant DNA molecules in heterologous host cells, as well as partially or substantially purified DNA molecules in solution. "Isolated" nucleic acid molecules also encompass *in vivo* and *in vitro* RNA transcripts of the DNA molecules of the present invention. An isolated nucleic acid molecule or nucleotide sequence can include a nucleic acid molecule or nucleotide sequence that is synthesized chemically or by recombinant means. Therefore, recombinant DNA contained in a vector are included in the definition of "isolated" as used herein.

Isolated nucleotide molecules also include recombinant DNA molecules in heterologous organisms, as well as partially or substantially purified DNA molecules in solution. *In vivo* and *in vitro* RNA transcripts of the DNA molecules of the present invention are also encompassed by "isolated" nucleotide sequences. Such isolated nucleotide sequences are useful in the manufacture of the encoded polypeptide, as probes for isolating homologous sequences (*e.g.*, from other mammalian species), for gene mapping (*e.g.*, by *in situ* hybridization with chromosomes), or for detecting expression of the gene in tissue (*e.g.*, human tissue), such as by Northern blot analysis.

The present invention also pertains to variant *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleic acid molecules that are not necessarily found in nature but that encode an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide. Thus, for

example, DNA molecules that comprise a sequence that is different from the naturally-occurring *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleotide sequence but which, due to the degeneracy of the genetic code, encode an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or
5 *HDRP(ΔNLS)* polypeptide of the present invention are also the subject of this invention.

The invention also encompasses *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleotide sequences encoding portions (fragments), or encoding variant polypeptides such as analogues or derivatives of an
10 *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide. Such variants can be naturally-occurring, such as in the case of allelic variation or single nucleotide polymorphisms, or non-naturally-occurring, such as those induced by various mutagens and mutagenic processes. Intended variations include, but are not limited to, addition, deletion, and substitution of one or more
15 nucleotides that can result in conservative or non-conservative amino acid changes, including additions and deletions. Preferably, the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleotide (and/or resultant amino acid) changes are silent or conserved; that is, they do not alter the characteristics or activity of the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*,
20 *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide. In one preferred embodiment, the nucleotide sequences are fragments that comprise one or more polymorphic microsatellite markers.

Other alterations of the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecules of the invention can
25 include, for example, labeling, methylation, internucleotide modifications such as uncharged linkages (*e.g.*, methyl phosphonates, phosphotriesters, phosphoamidates, and carbamates), charged linkages (*e.g.*, phosphorothioates or phosphorodithioates), pendent moieties (*e.g.*, polypeptides), intercalators (*e.g.*, acridine or psoralen), chelators, alkylators, and modified linkages (*e.g.*, alpha anomeric nucleic acids).
30 Also included are synthetic molecules that mimic nucleic acid molecules in the ability to bind to a designated sequences via hydrogen bonding and other chemical

interactions. Such molecules include, for example, those in which peptide linkages substitute for phosphate linkages in the backbone of the molecule.

The invention also pertains to *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleic acid molecules that hybridize under
5 high stringency hybridization conditions, such as for selective hybridization, to a nucleotide sequence described herein (e.g., nucleic acid molecules that specifically hybridize to a nucleotide sequence encoding polypeptides described herein, and, optionally, have an activity of the polypeptide). In one embodiment, the invention includes variants described herein that hybridize under high stringency hybridization
10 conditions (e.g., for selective hybridization) to a nucleotide sequence comprising a nucleotide sequence selected from SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9 and the complement of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9. In another embodiment, the invention includes variants described herein that hybridize under high stringency
15 hybridization conditions (e.g., for selective hybridization) to a nucleotide sequence encoding an amino acid sequence of SEQ ID NO: 2 (*HDAC9*), SEQ ID NO: 4 (*HDAC9a*), SEQ ID NO: 6 (*HDAC9(ΔNLS)*), SEQ ID NO: 8 (*HDAC9a(ΔNLS)*), or SEQ ID NO: 10 (*HDRP(ΔNLS)*). In a preferred embodiment, the variant that hybridizes under high stringency hybridizations encodes a polypeptide that has a
20 biological activity of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide (e.g., histone deacetylase activity or transcription repression activity).

Such nucleic acid molecules can be detected and/or isolated by specific hybridization (e.g., under high stringency conditions). "Specific hybridization," as
25 used herein, refers to the ability of a first nucleic acid to hybridize to a second nucleic acid in a manner such that the first nucleic acid does not hybridize to any nucleic acid other than to the second nucleic acid (e.g., when the first nucleic acid has a higher similarity to the second nucleic acid than to any other nucleic acid in a sample wherein the hybridization is to be performed). "Stringency conditions" for
30 hybridization is a term of art that refers to the incubation and wash conditions, e.g., conditions of temperature and buffer concentration, that permit hybridization of a particular nucleic acid to a second nucleic acid; the first nucleic acid may be

- perfectly (*i.e.*, 100%) complementary to the second, or the first and second may share some degree of complementarity that is less than perfect (*e.g.*, 70%, 75%, 85%, 95%). For example, certain high stringency conditions can be used that distinguish perfectly complementary nucleic acids from those of less
- 5 complementarity. "High stringency conditions," "moderate stringency conditions," and "low stringency conditions" for nucleic acid hybridizations are explained on pages 2.10.1-2.10.16 and pages 6.3.1-6.3.6 in *Current Protocols in Molecular Biology* (See Ausubel *et al.*, *supra*, the entire teachings of which are incorporated by reference herein). The exact conditions that determine the stringency of
- 10 hybridization depend not only on ionic strength (*e.g.*, 0.2XSSC or 0.1XSSC), temperature (*e.g.*, room temperature, 42°C or 68°C), and the concentration of destabilizing agents such as formamide or denaturing agents such as SDS, but also on factors such as the length of the nucleic acid sequence, base composition, percent mismatch between hybridizing sequences, and the frequency of occurrence of
- 15 subsets of that sequence within other non-identical sequences. Thus, equivalent conditions can be determined by varying one or more of these parameters while maintaining a similar degree of identity or similarity between the two nucleic acid molecules. Typically, conditions are used such that sequences at least about 60%, at least about 70%, at least about 80%, at least about 90% or at least about 95% or
- 20 more identical to each other remain hybridized to one another. By varying hybridization conditions from a level of stringency at which no hybridization occurs to a level at which hybridization is first observed, conditions that will allow a given sequence to hybridize (*e.g.*, selectively) with the most similar sequences in the sample can be determined.
- 25 Exemplary conditions are described in Krause and Aaronson, *Methods in Enzymology*, 200:546-556 (1991). Also, in, Ausubel, *et al.*, *supra*, which describes the determination of washing conditions for moderate or low stringency conditions. Washing is the step in which conditions are usually set so as to determine a minimum level of complementarity of the hybrids. Generally, starting from the
- 30 lowest temperature at which only homologous hybridization occurs, each °C by which the final wash temperature is reduced (holding SSC concentration constant) allows an increase by 1% in the maximum extent of mismatching among the

sequences that hybridize. Generally, doubling the concentration of SSC results in an increase in T_m of 17°C. Using these guidelines, the washing temperature can be determined empirically for high, moderate, or low stringency, depending on the level of mismatch sought.

5 For example, a low stringency wash can comprise washing in a solution containing 0.2XSSC/0.1% SDS for 10 minutes at room temperature; a moderate stringency wash can comprise washing in a prewarmed solution (42°C) solution containing 0.2XSSC/0.1% SDS for 15 minutes at 42°C; and a high stringency wash can comprise washing in prewarmed (68°C) solution containing 0.1XSSC/0.1%SDS
10 for 15 minutes at 68°C. Furthermore, washes can be performed repeatedly or sequentially to obtain a desired result as known in the art. Equivalent conditions can be determined by varying one or more of the parameters given as an example, as known in the art, while maintaining a similar degree of identity or similarity between the target nucleic acid molecule and the primer or probe used.

15 To determine the percent homology or identity of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of one polypeptide or nucleic acid molecule for optimal alignment with the other polypeptide or nucleic acid molecule). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide
20 positions are then compared, as described above.

The present invention also provides isolated *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleic acid molecules that contain a fragment or portion that hybridizes under highly stringent conditions to a nucleotide sequence comprising a nucleotide sequence selected from SEQ ID NO: 1,
25 SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, and the complement of any of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9 and also provides isolated nucleic acid molecules that contain a fragment or portion that hybridizes under highly stringent conditions to a nucleotide sequence encoding an amino acid sequence selected from SEQ ID NO: 2, SEQ ID NO: 4, SEQ
30 ID NO: 6, SEQ ID NO: 8, and SEQ ID NO: 10. The nucleic acid fragments of the invention are at least about 15, preferably, at least about 18, 20, 23, or 25 nucleotides, and can be 30, 40, 50, 100, 200 or more nucleotides in length. Longer

fragments, for example, 30 or more nucleotides in length, that encode antigenic polypeptides described herein are particularly useful, such as for the generation of antibodies as described above.

In a related aspect, the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*,
5 and *HDRP(ΔNLS)* nucleic acid fragments of the invention are used as probes or primers in assays such as those described herein. "Probes" or "primers" are oligonucleotides that hybridize in a base-specific manner to a complementary strand of nucleic acid molecules. Such probes and primers include polypeptide nucleic acids, as described in Nielsen *et al.*, Science, 254, 1497-1500 (1991). As also used
10 herein, the term "primer" in particular refers to a single-stranded oligonucleotide that acts as a point of initiation of template-directed DNA synthesis using well-known methods (*e.g.*, PCR, LCR) including, but not limited to those described herein.

Typically, a probe or primer comprises a region of nucleotide sequence that hybridizes to at least about 15, typically about 20-25, and more typically about 40,
15 50 or 75, consecutive nucleotides of a nucleic acid molecule comprising a contiguous nucleotide sequence selected from: SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, the complement of any of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, and a sequence encoding an amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6,
20 SEQ ID NO: 8, or SEQ ID NO: 10.

In preferred embodiments, a probe or primer comprises 100 or fewer nucleotides, preferably, from 6 to 50 nucleotides, and more preferably, from 12 to 30 nucleotides. In other embodiments, the probe or primer is at least 70% identical to the contiguous nucleotide sequence or to the complement of the contiguous
25 nucleotide sequence, preferably, at least 80% identical, more preferably, at least 90% identical, even more preferably, at least 95% identical, or even capable of selectively hybridizing to the contiguous nucleotide sequence or to the complement of the contiguous nucleotide sequence. Often, the probe or primer further comprises a label, *e.g.*, radioisotope, fluorescent compound, enzyme, or enzyme co-factor.

30 The nucleic acid molecules of the invention such as those described above can be identified and isolated using standard molecular biology techniques and the sequence information provided in SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5,

SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, and/or SEQ ID NO: 10. For example, nucleic acid molecules can be amplified and isolated by the polymerase chain reaction using synthetic oligonucleotide primers designed based on one or more of the nucleic acid sequences provided above and/or the complement of those sequences. Or such nucleic acid molecules may be designed based on nucleotide sequences encoding one or more of the amino acid sequences provided in SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10. See generally PCR Technology: Principles and Applications for DNA Amplification (ed. H.A. Erlich, Freeman Press, NY, NY, (1992); PCR Protocols: A Guide to Methods and Applications (Eds. Innis *et al.*, Academic Press, San Diego, CA, (1990); Mattila *et al.*, Nucleic Acids Res., 19: 4967 (1991); Eckert *et al.*, PCR Methods and Applications, 1: 17 (1991); PCR (eds. McPherson *et al.*, IRL Press, Oxford)); and U.S. Patent No. 4,683,202. The nucleic acid molecules can be amplified using cDNA, mRNA, or genomic DNA as a template, cloned into an appropriate vector and characterized by DNA sequence analysis.

Other suitable amplification methods include the ligase chain reaction (LCR) (See Wu and Wallace, Genomics, 4:560 (1989), Landegren *et al.*, Science, 241:1077 (1988)), transcription amplification (Kwoh *et al.*, Proc. Natl. Acad. Sci. USA, 86:1173 (1989)), and self-sustained sequence replication (See Guatelli *et al.*, Proc. Nat. Acad. Sci. USA, 87:1874 (1990)) and nucleic acid based sequence amplification (NASBA). The latter two amplification methods involve isothermal reactions based on isothermal transcription, that produce both single stranded RNA (ssRNA) and double stranded DNA (dsDNA) as the amplification products in a ratio of about 30 or 100 to 1, respectively.

The amplified DNA can be radiolabeled and used as a probe for screening a cDNA library derived from human cells, mRNA in zap express, ZIPLOX, or other suitable vector. Corresponding clones can be isolated, DNA can be obtained following *in vivo* excision, and the cloned insert can be sequenced in either or both orientations by art-recognized methods to identify the correct reading frame encoding a polypeptide of the appropriate molecular weight. For example, the direct analysis of the nucleotide sequence of nucleic acid molecules of the present

invention can be accomplished using well-known methods that are commercially available. See, for example, Sambrook *et al.*, Molecular Cloning, A Laboratory Manual (2nd Ed., CSHP, New York (1989)); Zyskind *et al.*, Recombinant DNA Laboratory Manual, (Acad. Press, (1988)). Using these or similar methods, the
5 polypeptide and the DNA encoding the polypeptide can be isolated, sequenced, and further characterized.

Antisense nucleic acid molecules of the invention can be designed using the nucleotide sequences of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9 and/or the complement of any of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9 and/or a portion of those
10 sequences, and/or the complement of those portion or sequences, and/or a sequence encoding the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, or encoding a portion of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10. Such antisense nucleic acid molecules can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid molecule (*e.g.*, an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability
15 of the duplex formed between the antisense and sense nucleic acids, *e.g.*, phosphorothioate derivatives and acridine substituted nucleotides can be used. Alternatively, the antisense nucleic acid molecule can be produced biologically using an expression vector into which a nucleic acid molecule has been subcloned in an antisense orientation (*i.e.*, RNA transcribed from the inserted nucleic acid molecule will be of an antisense orientation to a target nucleic acid of interest).
25

In general, the isolated *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleic acid sequences of the invention can be used as molecular weight markers on Southern blots, and as chromosome markers that are labeled to map related gene positions. The nucleic acid sequences can also be used to compare
30 with endogenous DNA sequences in patients to identify genetic disorders (*e.g.*, a predisposition for or susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease), and as probes, such as to hybridize and

discover related DNA sequences or to subtract out known sequences from a sample. The nucleic acid molecules of the present invention can also be used as therapeutic agents.

By a "cell proliferation disease" is meant a disease that is caused by or results in undesirably high levels of cell division, undesirably low levels of apoptosis, or both. For example, cancers such as lymphoma, leukemia, melanoma, ovarian cancer, breast cancer, pancreatic cancer, prostate cancer, colon cancer, and lung cancer are all examples of cell proliferation diseases. Myeloproliferative disorders, including polycythemia vera, essential thrombocythemia, agnogenic myeloid metaplasia, and chronic myelogenous leukemia are also cell proliferation diseases.

By a "cell differentiation disease" is meant a disease that is caused by or results in undesirably low levels of cell differentiation, or by undesirably high levels of cell differentiation. For example, cancers such as lymphoma, leukemia, melanoma, ovarian cancer, breast cancer, pancreatic cancer, prostate cancer, colon cancer, and lung cancer are all examples of cell differentiation diseases. Myeloproliferative disorders, including polycythemia vera, essential thrombocythemia, agnogenic myeloid metaplasia, and chronic myelogenous leukemia are also cell differentiation diseases.

By an "apoptotic disease" is meant a condition in which the apoptotic response is abnormal. This may pertain to a cell or a population of cells that does not undergo cell death under appropriate conditions. For example, normally a cell will die upon exposure to apoptotic-triggering agents, such as chemotherapeutic agents, or ionizing radiation. When, however, a subject has an apoptotic disease, for example, cancer, the cell or a population of cells may not undergo cell death in response to contact with apoptotic-triggering agents. In addition, a subject may have an apoptotic disease when the occurrence of cell death is too low, for example, when the number of proliferating cells exceeds the number of cells undergoing cell death, as occurs in cancer when such cells do not properly differentiate.

An apoptotic disease may also be a condition characterized by the occurrence of undesirably high levels of apoptosis. For example, certain neurodegenerative diseases, including but not limited to Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, restenosis, stroke, and ischemic

brain injury are apoptotic diseases in which neuronal cells undergo undesired cell death.

Other diseases for which the polypeptides and nucleic acid molecules of the present invention may be useful for diagnosing and/or treating include, but are not
5 limited to Huntington's disease.

The *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleic acid molecules of the present invention can further be used to derive primers for genetic fingerprinting, to raise anti-polypeptide antibodies using DNA immunization techniques, and as an antigen to raise anti-DNA antibodies or
10 elicit immune responses. Portions or fragments of the nucleotide sequences identified herein (and the corresponding complete gene sequences) can be used in numerous ways as polynucleotide reagents. For example, these sequences can be used to: (i) map their respective genes on a chromosome; and, thus, locate gene regions associated with genetic disease; (ii) identify an individual from a minute
15 biological sample (tissue typing); and (iii) aid in forensic identification of a biological sample.

In addition, the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleotide sequences of the invention can be used to identify and express recombinant polypeptides for analysis, characterization, or therapeutic use,
20 or as markers for tissues in which the corresponding polypeptide is expressed, either constitutively, during tissue differentiation, or in diseased states. The nucleic acid sequences can additionally be used as reagents in the screening and/or diagnostic assays described herein, and can also be included as components of kits (e.g., reagent kits) for use in the screening and/or diagnostic assays described herein.

25 Standard techniques, such as the polymerase chain reaction (PCR) and DNA hybridization, may be used to clone *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* homologs in other species, for example, mammalian homologs. *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* homologs may be readily identified using low-stringency DNA
30 hybridization or low-stringency PCR with human *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* probes or primers. Degenerate primers encoding human *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or

HDRP(Δ NLS) polypeptides may be used to clone *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* homologs by RT-PCR.

Alternatively, additional *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* homologs can be identified by utilizing
5 consensus sequence information for *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* polypeptides to search for similar polypeptides in other species. For example, polypeptide databases for other species can be searched for proteins with the HDAC domains described herein. Candidate polypeptides containing such a motif can then be tested for their *HDAC9*, *HDAC9a*,
10 *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* biological activities, using methods described herein.

EXPRESSION OF THE NUCLEIC ACID MOLECULES OF THE INVENTION

Another aspect of the invention pertains to nucleic acid constructs containing
15 an *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* nucleic acid molecule, for example, one selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, and the complement of any of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9 (or portions thereof). Yet another aspect of the invention
20 pertains to *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, and *HDRP(Δ NLS)* nucleic acid constructs containing a nucleic acid molecule encoding the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10. The constructs comprise a vector (*e.g.*, an expression vector) into which a sequence of the invention has been inserted in a sense or antisense orientation.

25 As used herein, the term "vector" or "construct" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid," which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral
30 genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal

mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors, expression vectors, are capable of directing the expression of genes to which they are operably linked. In general, expression vectors of utility in

- 5 recombinant DNA techniques are often in the form of plasmids. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses) that serve equivalent functions.

- Preferred recombinant expression vectors of the invention comprise a nucleic acid molecule of the invention in a form suitable for expression of the nucleic acid molecule in a host cell. This means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operably linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner that allows for expression of the nucleotide sequence (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals).
- 20 Such regulatory sequences are described, for example, in Goeddel, Gene Expression Technology: Methods in Enzymology 185, Academic Press, San Diego, CA (1990). Regulatory sequences include those that direct constitutive expression of a nucleotide sequence in many types of host cell and those that direct expression of the nucleotide sequence only in certain host cells (*e.g.*, tissue-specific regulatory
- 25 sequences).

- It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed and the level of expression of polypeptide desired. The expression vectors of the invention can be introduced into host cells to thereby produce
- 30 polypeptides, including fusion polypeptides, encoded by nucleic acid molecules as described herein.

The recombinant expression vectors of the invention can be designed for expression of a polypeptide of the invention in prokaryotic or eukaryotic cells, *e.g.*, bacterial cells, such as *E. coli*, insect cells (using baculovirus expression vectors), yeast cells or mammalian cells. Suitable host cells are discussed further in Goeddel, 5 *supra*. Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example, using T7 promoter regulatory sequences and T7 polymerase.

Another aspect of the invention pertains to host cells into which a recombinant expression vector of the invention has been introduced. The terms 10 "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but also to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included 15 within the scope of the term as used herein.

A host cell can be any prokaryotic or eukaryotic cell. For example, a nucleic acid molecule of the invention can be expressed in bacterial cells (*e.g.*, *E. coli*), insect cells, yeast, or mammalian cells (such as Chinese hamster ovary cells (CHO) or COS cells, human 293T cells, HeLa cells, NIH 3T3 cells, and mouse 20 erythroleukemia (MEL) cells). Other suitable host cells are known to those skilled in the art.

Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of 25 art-recognized techniques for introducing a foreign nucleic acid molecule (*e.g.*, DNA) into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, *et al.* (*supra*), and other laboratory manuals.

30 For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select

these integrants, a gene that encodes a selectable marker (*e.g.*, for resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Preferred selectable markers include those that confer resistance to drugs, such as G418, hygromycin, or methotrexate. Nucleic acid molecules encoding a selectable
5 marker can be introduced into a host cell on the same vector as the nucleic acid molecule of the invention or can be introduced on a separate vector. Cells stably transfected with the introduced nucleic acid molecule can be identified by drug selection (*e.g.*, cells that have incorporated the selectable marker gene will survive, while the other cells die).

- 10 A host cell of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce (*i.e.*, express) a polypeptide of the invention. Accordingly, the invention further provides methods for producing a polypeptide using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of invention (into which a recombinant expression vector
15 encoding a polypeptide of the invention has been introduced) in a suitable medium such that the polypeptide is produced. In another embodiment, the method further comprises isolating the polypeptide from the medium or the host cell.

- The host cells of the invention can also be used to produce nonhuman transgenic animals. For example, in one embodiment, a host cell of the invention is
20 a fertilized oocyte or an embryonic stem cell into which an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule of the invention has been introduced. Such host cells can then be used to create non-human transgenic animals in which exogenous nucleotide sequences have been introduced into the genome or homologous recombinant animals in which
25 endogenous nucleotide sequences have been altered. Such animals are useful for studying the function and/or activity of the nucleotide sequence and polypeptide encoded by the sequence and for identifying and/or evaluating modulators of their activity.

- As used herein, a “transgenic animal” is a non-human animal, preferably, a
30 mammal, more preferably, a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens, and amphibians. A

transgene is exogenous DNA that is integrated into the genome of a cell from which a transgenic animal develops and that remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, a “homologous recombina-
5 recombinant animal” is a non-human animal, preferably, a mammal, more preferably, a mouse, in which an endogenous gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, *e.g.*, an embryonic cell of the animal, prior to development of the animal.

10 Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, U.S. Patent No. 4,873,191, and in Hogan, *Manipulating the Mouse Embryo* (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., (1986)). Methods for
15 constructing homologous recombination vectors and homologous recombinant animals are described further in Bradley, *Current Opinion in Bio/Technology*, 2:823-829 (1991) and in PCT Publication Nos. WO 90/11354, WO 91/01140, WO 92/0968, and WO 93/04169. Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut *et al.*,
20 *Nature*, 385:810-813 (1997) and PCT Publication Nos. WO 97/07668 and WO 97/07669.

ANTIBODIES OF THE INVENTION

Polyclonal and/or monoclonal antibodies that selectively bind one form of an
25 HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide but not another form of the polypeptide are also provided. Antibodies are also provided that bind a portion of either the variant or reference HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide that contains the polymorphic site or sites.

30 In another aspect, the invention provides antibodies to each of the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), and HDRP(Δ NLS) polypeptides and polypeptide fragments of the invention, *e.g.*, having an amino acid sequence encoded

by SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, or a portion thereof, or having an amino acid sequence encoded by a nucleic acid molecule comprising all or a portion of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9, (*e.g.*, SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10, or another variant, or portion thereof).

The term "purified antibody" as used herein refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site that selectively binds an antigen. A molecule that selectively binds to a polypeptide of the invention is a molecule that binds to that polypeptide or a fragment thereof, but does not substantially bind other molecules in a sample, *e.g.*, a biological sample that naturally contains the polypeptide. Preferably the antibody is at least 60%, by weight, free from proteins and naturally occurring organic molecules with which it naturally associated. More preferably, the antibody preparation is at least 75% or 90%, and most preferably, 99%, by weight, antibody. Examples of immunologically active portions of immunoglobulin molecules include F(ab) and F(ab')₂ fragments that can be generated by treating the antibody with an enzyme such as pepsin.

The invention provides polyclonal and monoclonal antibodies that selectively bind to an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide of the invention. The term "monoclonal antibody" or "monoclonal antibody composition," as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope of a polypeptide of the invention. A monoclonal antibody composition thus typically displays a single binding affinity for a particular polypeptide of the invention with which it immunoreacts.

Polyclonal antibodies can be prepared as described above by immunizing a suitable subject with a desired immunogen, *e.g.*, an HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptide of the invention or fragment thereof. The antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized polypeptide. If desired, the antibody molecules directed against the polypeptide can be isolated from the mammal (*e.g.*, from the

blood) and further purified by well-known techniques, such as protein A chromatography to obtain the IgG fraction.

At an appropriate time after immunization, *e.g.*, when the antibody titers are highest, antibody-producing cells can be obtained from the subject and used to
5 prepare monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein, *Nature*, 256:495-497 (1975), the human B cell hybridoma technique (Kozbor *et al.*, *Immunol. Today*, 4:72 (1983)), the EBV-hybridoma technique (Cole *et al.*, *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., pp. 77-96 (1985)) or trioma techniques. The
10 technology for producing hybridomas is well known (see generally *Current Protocols in Immunology*, Coligan *et al.*, (eds.) John Wiley & Sons, Inc., New York, NY (1994)). Briefly, an immortal cell line (typically a myeloma) is fused to lymphocytes (typically splenocytes) from a mammal immunized with an immunogen as described above, and the culture supernatants of the resulting hybridoma cells are screened to
15 identify a hybridoma producing a monoclonal antibody that binds a polypeptide of the invention.

Any of the many well known protocols used for fusing lymphocytes and immortalized cell lines can be applied for the purpose of generating a monoclonal antibody to a polypeptide of the invention (see, *e.g.*, *Current Protocols in Immunology*, *supra*; Galfre *et al.*, (1977) *Nature*, 266:55052; R.H. Kenneth, in *Monoclonal Antibodies: A New Dimension In Biological Analyses*, Plenum
20 Publishing Corp., New York, New York (1980); and Lerner, *Yale J. Biol. Med.*, 54:387-402 (1981)). Moreover, the ordinarily skilled worker will appreciate that there are many variations of such methods that also would be useful.

25 Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody to an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide of the invention can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (*e.g.*, an antibody phage display library) with the polypeptide to thereby isolate immunoglobulin
30 library members that bind the polypeptide. Kits for generating and screening phage display libraries are commercially available (*e.g.*, the Pharmacia Recombinant Phage Antibody System, Catalog No. 27-9400-01; and the Stratagene SurfZAP™ Phage

Display Kit, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, U.S. Patent No. 5,223,409; PCT Publication No. WO 92/18619; PCT Publication No. WO 91/17271; PCT Publication No. WO 92/20791; PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT Publication No. WO 92/01047; PCT Publication No. WO 92/09690; PCT Publication No. WO 90/02809; Fuchs *et al.*, *Bio/Technology*, 9:1370-1372 (1991); Hay *et al.*, *Hum. Antibod. Hybridomas*, 3:81-85 (1992); Huse *et al.*, *Science*, 246:1275-1281 (1989); and Griffiths *et al.*, *EMBO J.*, 12:725-734 (1993).

10 Additionally, recombinant antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, are within the scope of the invention. Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art.

15 In general, antibodies of the invention (*e.g.*, a monoclonal antibody) can be used to isolate an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide of the invention by standard techniques, such as affinity chromatography or immunoprecipitation. A polypeptide-specific antibody can facilitate the purification of natural polypeptide from cells and of recombinantly produced polypeptide expressed in host cells. Moreover, an antibody specific for an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide of the invention can be used to detect the polypeptide (*e.g.*, in a cellular lysate, cell supernatant, or tissue sample) in order to evaluate the abundance and pattern of expression of the polypeptide.

25 The antibodies of the present invention can also be used diagnostically to monitor protein levels in tissue as part of a clinical testing procedure, *e.g.*, to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β -galactosidase, and acetylcholinesterase; examples of suitable

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prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride and phycoerythrin; an example of a luminescent material includes luminol; examples of
5 bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I , ^{131}I , ^{35}S , and ^3H .

DIAGNOSTIC AND SCREENING ASSAYS OF THE INVENTION

The present invention also pertains to diagnostic assays for assessing *HDAC*
10 *9 HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* gene expression, or for assessing activity of HDAC9, HDAC9a, HDAC9(ΔNLS), HDAC9a(ΔNLS), or HDRP(ΔNLS) polypeptides of the invention. In one embodiment, the assays are used in the context of a biological sample (*e.g.*, blood, serum, cells, tissue) to thereby determine whether an individual is afflicted with a cell proliferation disease,
15 an apoptotic disease, or a cell differentiation disease, or is at risk for (has a predisposition for or a susceptibility to) developing a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. The invention also provides for prognostic (or predictive) assays for determining whether an individual is susceptible to developing a cell proliferation disease, an apoptotic disease, or a cell
20 differentiation disease. For example, mutations in the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule can be assayed in a biological sample. Such assays can be used for prognostic or predictive purpose to thereby prophylactically treat an individual prior to the onset of symptoms associated with a cell proliferation disease, an apoptotic disease, or a cell
25 differentiation disease.

Another aspect of the invention pertains to assays for monitoring the influence of agents, or candidate compounds (*e.g.*, drugs or other agents) on the nucleic acid molecule expression or biological activity of polypeptides of the invention, as well as to assays for identifying candidate compounds that bind to an
30 HDAC9, HDAC9a polypeptide, an HDAC9(ΔNLS) polypeptide, an HDAC9a(ΔNLS) polypeptide, or an HDRP(ΔNLS) polypeptide. These and other assays and agents are described in further detail in the following sections.

DIAGNOSTIC ASSAYS

HDAC9, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecules, probes, primers, polypeptides, and antibodies to an *HDAC9*,
5 an *HDAC9a* protein, an *HDAC9(ΔNLS)* protein, an *HDAC9a(ΔNLS)* protein, or an *HDRP(ΔNLS)* protein can be used in methods of diagnosis of a susceptibility to, or likelihood of having a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, as well as in kits useful for diagnosis of a susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

10 In one embodiment of the invention, diagnosis of a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease is made by detecting a polymorphism in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. The polymorphism can be a mutation in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, such as the
15 insertion or deletion of a single nucleotide, or of more than one nucleotide, resulting in a frame shift mutation; the change of at least one nucleotide, resulting in a change in the encoded amino acid; the change of at least one nucleotide, resulting in the generation of a premature stop codon; the deletion of several nucleotides, resulting in a deletion of one or more amino acids encoded by the nucleotides; the insertion of
20 one or several nucleotides, such as by unequal recombination or gene conversion, resulting in an interruption of the coding sequence of the gene; duplication of all or a part of the gene; transposition of all or a part of the gene; or rearrangement of all or a part of the gene, or a change in the expression pattern of the various *HDAC9* isoforms. More than one such mutation may be present in a single nucleic acid
25 molecule.

Such sequence changes cause a mutation in the polypeptide encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. For example, if the mutation is a frame shift mutation, the frame shift can result in a change in the encoded amino acids, and/or can result in the generation of a
30 premature stop codon, causing generation of a truncated polypeptide. Alternatively, a polymorphism associated with a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease can be a synonymous

mutation in one or more nucleotides (*i.e.*, a mutation that does not result in a change in the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide). Such a polymorphism may alter sites, affect the stability or transport of mRNA, or otherwise affect the transcription or translation of the nucleic acid molecule. HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) that has any of the mutations described above is referred to herein as a "mutant nucleic acid molecule."

In a first method of diagnosing a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, hybridization methods, such as Southern analysis, Northern analysis, or *in situ* hybridizations, can be used (see Ausubel, *et al.*, *supra*). For example, a biological sample from a test subject (a "test sample") of genomic DNA, RNA, or cDNA, is obtained from an individual suspected of having, being susceptible to or predisposed for, or carrying a defect for, a cell proliferation disease, an apoptotic disease, or a cell differentiation disease (the "test individual"). The individual can be an adult, child, or fetus. The test sample can be from any source that contains genomic DNA, such as a blood sample, sample of amniotic fluid, sample of cerebrospinal fluid, or tissue sample from skin, muscle, buccal or conjunctival mucosa, placenta, gastrointestinal tract, or other organs. A test sample of DNA from fetal cells or tissue can be obtained by appropriate methods, such as by amniocentesis or chorionic villus sampling. The DNA, RNA, or cDNA sample is then examined to determine whether a polymorphism in HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) is present, and/or to determine which variant(s) encoded by HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) is present. The presence of the polymorphism or variant(s) can be indicated by hybridization of the gene in the genomic DNA, RNA, or cDNA to a nucleic acid probe. A "nucleic acid probe," as used herein, can be a DNA probe or an RNA probe; the nucleic acid probe can contain at least one polymorphism in HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) or contains a nucleic acid encoding a particular variant of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS). The probe can be any of the nucleic acid

molecules described above (e.g., the entire nucleic acid molecule, a fragment, a vector comprising the gene, a probe, or primer, etc.).

To diagnose a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, a hybridization sample is formed by contacting the test sample containing *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, with at least one nucleic acid probe. A preferred probe for detecting mRNA or genomic DNA is a labeled nucleic acid probe capable of hybridizing to *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* mRNA or genomic DNA sequences described herein. The nucleic acid probe can be, for example, a full-length nucleic acid molecule, or a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250, or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to appropriate mRNA or genomic DNA. For example, the nucleic acid probe can be all or a portion of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, or the complement of SEQ ID NO: 1 or SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9; or can be a nucleic acid molecule encoding all or a portion of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10. Other suitable probes for use in the diagnostic assays of the invention are described above (see, e.g., probes and primers discussed under the heading, "Nucleic Acids of the Invention").

The hybridization sample is maintained under conditions that are sufficient to allow specific hybridization of the nucleic acid probe to *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. "Specific hybridization," as used herein, indicates exact hybridization (e.g., with no mismatches). Specific hybridization can be performed under high stringency conditions or moderate stringency conditions, for example, as described above. In a particularly preferred embodiment, the hybridization conditions for specific hybridization are high stringency.

Specific hybridization, if present, is then detected using standard methods. If specific hybridization occurs between the nucleic acid probe and *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* in the test sample, then *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* has the

polymorphism, or is the variant, that is present in the nucleic acid probe. More than one nucleic acid probe can also be used concurrently in this method. Specific hybridization of any one of the nucleic acid probes is indicative of a polymorphism in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, or of the presence of a particular variant encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, and is therefore diagnostic for a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

In Northern analysis (see Current Protocols in Molecular Biology, Ausubel, *et al.*, *supra*), the hybridization methods described above are used to identify the presence of a polymorphism or of a particular variant, associated with a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. For Northern analysis, a test sample of RNA is obtained from the individual by appropriate means. Specific hybridization of a nucleic acid probe, as described above, to RNA from the individual is indicative of a polymorphism in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, or of the presence of a particular variant encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, and is therefore diagnostic for a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

For representative examples of use of nucleic acid probes, see, for example, U.S. Patent Nos. 5,288,611 and 4,851,330.

Alternatively, a peptide nucleic acid (PNA) probe can be used instead of a nucleic acid probe in the hybridization methods described above. PNA is a DNA mimic having a peptide-like, inorganic backbone, such as N-(2-aminoethyl)glycine units, with an organic base (A, G, C, T, or U) attached to the glycine nitrogen via a methylene carbonyl linker (see, for example, Nielsen *et al.*, *Bioconjugate Chemistry*, 5 (1994), American Chemical Society, p. 1 (1994)). The PNA probe can be designed to specifically hybridize to a gene having a polymorphism associated with a susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. Hybridization of the PNA probe to *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* is diagnostic for a decreased

susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

In another method of the invention, mutation analysis by restriction digestion can be used to detect a mutant nucleic acid molecule, or nucleic acid molecules
5 containing a polymorphism(s), if the mutation or polymorphism in the gene results in the creation or elimination of a restriction site. A test sample containing genomic DNA is obtained from the individual. Polymerase chain reaction (PCR) can be used to amplify *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* (and, if necessary, the flanking sequences) in the test sample of genomic DNA from
10 the test individual. RFLP analysis is conducted as described (see Current Protocols in Molecular Biology, *supra*). The digestion pattern of the relevant DNA fragment indicates the presence or absence of the mutation or polymorphism in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, and therefore indicates the presence or absence of this decreased susceptibility to a cell
15 proliferation disease, an apoptotic disease, or a cell differentiation disease.

Sequence analysis can also be used to detect specific polymorphisms in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. A test sample of DNA or RNA is obtained from the test individual. PCR or other appropriate methods can be used to amplify the nucleic acid molecule, and/or its
20 flanking sequences, if desired. The sequence of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, or a fragment of the any of those nucleic acid molecules, or an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* cDNA, or a fragment of any of those cDNAs, or an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* mRNA,
25 or a fragment of any of those mRNAs, is determined, using standard methods. The sequence of the above gene, gene fragment, cDNA, cDNA fragment, mRNA, or mRNA fragment is compared with the known nucleic acid sequence of the nucleic acid molecule, cDNA (e.g., SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, or a nucleic acid sequence encoding the protein of SEQ ID
30 NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, or a fragment thereof) or mRNA, as appropriate. The presence of a polymorphism in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* indicates that the

individual has a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

Allele-specific oligonucleotides can also be used to detect the presence of a polymorphism in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or
5 *HDRP(ΔNLS)*, through the use of dot-blot hybridization of amplified oligonucleotides with allele-specific oligonucleotide (ASO) probes (see, for example, Saiki *et al.*, Nature (London) 324:163-166 (1986)). An "allele-specific oligonucleotide" (also referred to herein as an "allele-specific oligonucleotide probe") is an oligonucleotide of approximately 10-50 base pairs, preferably
10 approximately 15-30 base pairs, that specifically hybridizes to *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, and that contains a polymorphism associated with a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. An allele-specific oligonucleotide probe that is specific for particular polymorphisms in *HDAC9*,
15 *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* can be prepared, using standard methods (see Current Protocols in Molecular Biology, *supra*).

To identify polymorphisms in the gene that are associated with a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease a test sample of DNA is obtained from the individual. PCR
20 can be used to amplify all or a fragment of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, and its flanking sequences. The DNA containing the amplified *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* (or a fragment of any of those genes) is dot-blotted, using standard methods (see Current Protocols in Molecular Biology, *supra*), and the blot is
25 contacted with the oligonucleotide probe. The presence of specific hybridization of the probe to the amplified *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* is then detected. Specific hybridization of an allele-specific oligonucleotide probe to DNA from the individual is indicative of a polymorphism in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, and is
30 therefore indicative of a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

In another embodiment, arrays of oligonucleotide probes that are complementary to target nucleic acid sequence segments from an individual, can be used to identify polymorphisms in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. For example, in one embodiment, an

5 oligonucleotide array can be used. Oligonucleotide arrays typically comprise a plurality of different oligonucleotide probes that are coupled to a surface of a substrate in different known locations. These oligonucleotide arrays, also described as "GENECHIPS™," have been generally described in the art, for example, U.S. Patent No. 5,143,854 and PCT patent publication Nos. WO 90/15070 and 92/10092.

10 These arrays can generally be produced using mechanical synthesis methods or light directed synthesis methods that incorporate a combination of photolithographic methods and solid phase oligonucleotide synthesis methods. See Fodor *et al.*, Science, 251:767-777 (1991), Pirrung *et al.*, U.S. Patent No. 5,143,854; PCT Publication No. WO 90/15070; Fodor *et al.*, PCT Publication No. WO 92/10092,

15 and U.S. Patent No. 5,424,186, the entire teachings of each of which are incorporated by reference herein. Techniques for the synthesis of these arrays using mechanical synthesis methods are described in, *e.g.*, U.S. Patent No. 5,384,261, the entire teachings of which are incorporated by reference herein.

Once an oligonucleotide array is prepared, a nucleic acid of interest is

20 hybridized to the array and scanned for polymorphisms. Hybridization and scanning are generally carried out by methods described herein and also in, *e.g.*, Published PCT Application Nos. WO 92/10092 and WO 95/11995, and U.S. Patent No. 5,424,186, the entire teachings of which are incorporated by reference herein. In brief, a target nucleic acid sequence that includes one or more previously identified

25 polymorphic markers is amplified by well known amplification techniques, *e.g.*, PCR. Typically, this involves the use of primer sequences that are complementary to the two strands of the target sequence both upstream and downstream from the polymorphism. Asymmetric PCR techniques may also be used. Amplified target, generally incorporating a label, is then hybridized with the array under appropriate

30 conditions. Upon completion of hybridization and washing of the array, the array is scanned to determine the position on the array to which the target sequence

hybridizes. The hybridization data obtained from the scan is typically in the form of fluorescence intensities as a function of location on the array.

Although primarily described in terms of a single detection block, *e.g.*, for detection of a single polymorphism, arrays can include multiple detection blocks, and thus be capable of analyzing multiple, specific polymorphisms. In alternate arrangements, it will generally be understood that detection blocks may be grouped within a single array or in multiple, separate arrays so that varying, optimal conditions may be used during the hybridization of the target to the array. For example, it may often be desirable to provide for the detection of those polymorphisms that fall within G-C rich stretches of a genomic sequence, separately from those falling in A-T rich segments. This allows for the separate optimization of hybridization conditions for each situation.

Additional descriptions of the use of oligonucleotide arrays for detection of polymorphisms can be found, for example, in U.S. Patent Nos. 5,858,659 and 5,837,832, the entire teachings of which are incorporated by reference herein.

Other methods of nucleic acid analysis can be used to detect polymorphisms in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* or variants encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. Representative methods include direct manual sequencing (Church and Gilbert *Proc. Natl. Acad. Sci. USA* 81: 1991-1995, (1988); Sanger *et al.*, *Proc. Natl. Acad. Sci.* 74: 5463-5467 (1977); Beavis *et al.*, U.S. Patent No. 5,288,644); automated fluorescent sequencing; single-stranded conformation polymorphism assays (SSCP); clamped denaturing gel electrophoresis (CDGE); denaturing gradient gel electrophoresis (DGGE) (Sheffield *et al.*, *Proc. Natl. Acad. Sci. USA* 86: 232-236 (1991)), mobility shift analysis (Orita *et al.*, *Proc. Natl. Acad. Sci. USA* 86: 2766-2770 (1989)), restriction enzyme analysis (Flavell *et al.*, *Cell* 15: 25 (1978); Geever, *et al.*, *Proc. Natl. Acad. Sci. USA* 78: 5081 (1981)); heteroduplex analysis; chemical mismatch cleavage (CMC) (Cotton *et al.*, *Proc. Natl. Acad. Sci. USA* 85: 4397-4401 (1985)); RNase protection assays (Myers *et al.*, *Science* 230: 1242 (1985)); use of polypeptides that recognize nucleotide mismatches, such as *E. coli* mutS protein; and allele-specific PCR.

In another embodiment of the invention, diagnosis of a susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease can also be made by examining the level of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid, for example, using in situ hybridization techniques known to one skilled in the art, or by examining the level of expression, activity, and/or composition of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide, by a variety of methods, including enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations, immunohistochemistry, and immunofluorescence. A test sample from an individual is assessed for the presence of an alteration in the level of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid or in the expression and/or an alteration in composition of the polypeptide encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, or for the presence of a particular variant encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. An alteration in expression of a polypeptide encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* can be, for example, an alteration in the quantitative polypeptide expression (*i.e.*, the amount of polypeptide produced); an alteration in the composition of a polypeptide encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, or an alteration in the qualitative polypeptide expression (*e.g.*, expression of a mutant *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide or variant thereof). In a preferred embodiment, diagnosis of a susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease is made by detecting a particular variant encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, or a particular pattern of variants. Preferably, increased levels of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* or increased expression or activity of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide, relative to a control sample, for example, a sample known not to be associated with a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, indicates an increased susceptibility or likelihood that the individual has a cell proliferation disease, an apoptotic disease, or a cell

differentiation disease. Alternatively, decreased levels of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* or decreased expression or activity of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide, relative to a control sample, for example, a sample

5 known not to be associated with a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, indicates a decreased susceptibility or likelihood that the individual has a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

Both quantitative and qualitative alterations can also be present. An

10 “alteration” or “modulation” in the polypeptide expression, activity, or composition, as used herein, refers to an alteration in expression or composition in a test sample, as compared with the expression or composition of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide in a control sample. A control sample is a sample that corresponds to the test sample (*e.g.*, is

15 from the same type of cells), and is from an individual who is not affected by a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. An alteration in the expression or composition of the polypeptide in the test sample, as compared with the control sample, is indicative of a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

20 Similarly, the presence of one or more different variants in the test sample, or the presence of significantly different amounts of different variants in the test sample, as compared with the control sample, is indicative of a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

It is understood that alterations or modulations in polypeptide expression or

25 function can occur in varying degrees. For example, an alteration or modulation in expression can be an increase, for example, by at least 1.5-fold to 2-fold, at least 3-fold, or, at least 5-fold, relative to the control. Alternatively, the alteration or modulation in polypeptide expression can be a decrease, for example, by at least 10%, at least 40%, 50%, or 75%, or by at least 90%, relative to the control.

30 Various means of examining expression or composition of the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide can be used, including spectroscopy, colorimetry, electrophoresis, isoelectric focusing, and

immunoassays (*e.g.*, David *et al.*, U.S. Patent No. 4,376,110) such as immunoblotting (see also Ausubel *et al.*, *supra*; particularly chapter 10). For example, in one embodiment, an antibody capable of binding to the polypeptide (*e.g.*, as described above), preferably an antibody with a detectable label, can be used. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (*e.g.*, Fab or F(ab')₂) can be used. The term "labeled," with regard to the antibody, is intended to encompass direct labeling of the antibody by coupling (*i.e.*, physically linking) a detectable substance to the antibody, as well as indirect labeling of the antibody by reacting it with another reagent that is directly labeled. An example of indirect labeling is detection of a primary antibody using a fluorescently labeled secondary antibody.

Western blotting analysis, using an antibody as described above that specifically binds to a mutant HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, or an antibody that specifically binds to a non-mutant HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, or an antibody that specifically binds to a particular variant encoded by *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)*, can be used to identify the presence in a test sample of a particular variant of a polypeptide encoded by a polymorphic or mutant *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)*, or the absence in a test sample of a particular variant or of a polypeptide encoded by a non-polymorphic or non-mutant gene. The presence of a polypeptide encoded by a polymorphic or mutant gene, or the absence of a polypeptide encoded by a non-polymorphic or non-mutant gene, is diagnostic for a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, as is the presence (or absence) of particular variants encoded by the *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* nucleic acid molecule.

In one embodiment of this method, the level or amount of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide in a test sample is compared with the level or amount of the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide in a control sample. A level or amount of the polypeptide in the test sample that is higher or

lower than the level or amount of the polypeptide in the control sample, such that the difference is statistically significant, is indicative of an alteration in the expression of the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, and is diagnostic for a decreased susceptibility to a cell proliferation
5 disease, an apoptotic disease, or a cell differentiation disease.

Alternatively, the composition of the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide in a test sample is compared with the composition of the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide in a control sample. A difference in the composition of
10 the polypeptide in the test sample, as compared with the composition of the polypeptide in the control sample (e.g., the presence of different variants), is diagnostic for a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. In another embodiment, both the level or amount and the composition of the polypeptide can be assessed in the test sample
15 and in the control sample. A difference in the amount or level of the polypeptide in the test sample, compared to the control sample; a difference in composition in the test sample, compared to the control sample; or both a difference in the amount or level, and a difference in the composition, is indicative of a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

20 Kits (e.g., reagent kits) useful in the methods of diagnosis comprise components useful in any of the methods described herein, including, for example, hybridization probes or primers as described herein (e.g., labeled probes or primers), reagents for detection of labeled molecules, restriction enzymes (e.g., for RFLP analysis), allele-specific oligonucleotides, antibodies that bind to a mutant or to
25 non-mutant (native) HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, means for amplification of nucleic acids comprising HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS), or means for analyzing the nucleic acid sequence of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS), or for analyzing the amino acid sequence of an
30 HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, etc.

SCREENING ASSAYS AND AGENTS IDENTIFIED THEREBY

The invention provides methods (also referred to herein as “screening assays”) for identifying the presence of a nucleotide that hybridizes to a nucleic acid of the invention, as well as for identifying the presence of a polypeptide encoded by a nucleic acid of the invention. In one embodiment, the presence (or absence) of a nucleic acid molecule of interest (*e.g.*, a nucleic acid that has significant homology with a nucleic acid of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*) in a sample can be assessed by contacting the sample with a nucleic acid comprising a nucleic acid of the invention (*e.g.*, a nucleic acid having the sequence of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9, which may optionally comprise at least one polymorphism, or the complement thereof, or a nucleic acid encoding an amino acid having the sequence of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10, or a fragment or variant of such nucleic acids), under stringent conditions as described above, and then assessing the sample for the presence (or absence) of hybridization. In a preferred embodiment, high stringency conditions are conditions appropriate for selective hybridization. In another embodiment, a sample containing the nucleic acid molecule of interest is contacted with a nucleic acid containing a contiguous nucleotide sequence (*e.g.*, a primer or a probe as described above) that is at least partially complementary to a part of the nucleic acid molecule of interest (*e.g.*, an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid), and the contacted sample is assessed for the presence or absence of hybridization. In a preferred embodiment, the nucleic acid containing a contiguous nucleotide sequence is completely complementary to a part of the nucleic acid molecule of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*.

In any of the above embodiments, all or a portion of the nucleic acid of interest can be subjected to amplification prior to performing the hybridization.

In another embodiment, the presence (or absence) of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide, such as a polypeptide of the invention or a fragment or variant thereof, in a sample can be assessed by contacting the sample with an antibody that specifically binds to the

polypeptide of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) (*e.g.*, an antibody such as those described above), and then assessing the sample for the presence (or absence) of binding of the antibody to the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide.

- 5 In another embodiment, the invention provides methods for identifying agents or compounds (*e.g.*, fusion proteins, polypeptides, peptidomimetics, prodrugs, receptors, binding agents, antibodies, small molecules or other drugs, or ribozymes) that alter or modulate (*e.g.*, increase or decrease) the activity of the polypeptides described herein, or that otherwise interact with the polypeptides
- 10 herein. For example, such compounds can be compounds or agents that bind to polypeptides described herein (*e.g.*, HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) substrates or agents); that have a stimulatory or inhibitory effect on, for example, activity of polypeptides of the invention; or that change (*e.g.*, enhance or inhibit) the ability of the polypeptides of the invention to
- 15 interact with HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) binding agents; or that alter post-translational processing of the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide (*e.g.*, agents that alter proteolytic processing to direct the polypeptide from where it is normally synthesized to another location in the cell, such as the cell
- 20 surface; or agents that alter proteolytic processing such that more polypeptide is released from the cell, etc.). In one example, the binding agent is a cell proliferation disease binding agent, an apoptotic disease binding agent, or a cell differentiation disease binding agent. As used herein, by a "cell proliferation disease binding agent," an "apoptotic disease binding agent," or a "cell differentiation disease
- 25 binding agent" is meant an agent as described herein that binds to a polypeptide of the present invention and modulates a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. The modulation can be an increase or a decrease in the severity or progression of the disease. In addition, a cell proliferation disease binding agent, an apoptotic disease binding agent, or a cell differentiation disease
- 30 binding agent includes an agent that binds to a polypeptide that is upstream (earlier) or downstream (later) of the cell signaling events mediated by a polypeptide of the

present invention, and thereby modulates the overall activity of the signaling pathway; in turn, the disease state is modulated.

The candidate compound can cause an increase in the activity of the polypeptide. For example, the activity of the polypeptide can be increased by at least
5 1.5-fold to 2-fold, at least 3-fold, or, at least 5-fold, relative to the control. Alternatively, the polypeptide activity can be a decrease, for example, by at least 10%, at least 20%, 40%, 50%, or 75%, or by at least 90%, relative to the control.

In one embodiment, the invention provides assays for screening candidate compounds or test agents to identify compounds that bind to or modulate the activity
10 of polypeptides described herein (or biologically active portion(s) thereof), as well as agents identifiable by the assays. As used herein, a "candidate compound" or "test agent" is a chemical molecule, be it naturally-occurring or artificially-derived, and includes, for example, peptides, proteins, synthesized molecules, for example, synthetic organic molecules, naturally-occurring molecule, for example, naturally
15 occurring organic molecules, nucleic acid molecules, and components thereof.

In general, candidate compounds for uses in the present invention may be identified from large libraries of natural products or synthetic (or semi-synthetic) extracts or chemical libraries according to methods known in the art. Those skilled in the field of drug discovery and development will understand that the precise
20 source of test extracts or compounds is not critical to the screening procedure(s) of the invention. Accordingly, virtually any number of chemical extracts or compounds can be screened using the exemplary methods described herein. Examples of such extracts or compounds include, but are not limited to, plant-, fungal-, prokaryotic- or animal-based extracts, fermentation broths, and synthetic compounds, as well as
25 modification of existing compounds. Numerous methods are also available for generating random or directed synthesis (e.g., semi-synthesis or total synthesis) of any number of chemical compounds, including, but not limited to, saccharide-, lipid-, peptide-, and nucleic acid-based compounds. Synthetic compound libraries are commercially available, e.g., from Brandon Associates (Merrimack, NH) and
30 Aldrich Chemical (Milwaukee, WI). Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant, and animal extracts are commercially available from a number of sources, including Biotics (Sussex, UK), Xenova

(Slough, UK), Harbor Branch Oceanographics Institute (Ft. Pierce, FL), and PharmaMar, U.S.A. (Cambridge, MA). In addition, natural and synthetically produced libraries are generated, if desired, according to methods known in the art, e.g., by standard extraction and fractionation methods. For example, candidate
5 compounds can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the "one-bead one-compound" library method; and synthetic library methods using affinity chromatography selection. The biological
10 library approach is limited to polypeptide libraries, while the other four approaches are applicable to polypeptide, non-peptide oligomer or small molecule libraries of compounds (Lam, Anticancer Drug Des., 12: 145 (1997)). Furthermore, if desired, any library or compound is readily modified using standard chemical, physical, or biochemical methods.

15 In addition, those skilled in the art of drug discovery and development readily understand that methods for dereplication (e.g., taxonomic dereplication, biological dereplication, and chemical dereplication, or any combination thereof) or the elimination of replicates or repeats of materials already known for their activities should be employed whenever possible.

20 When a crude extract is found to modulate (i.e., stimulate or inhibit) the expression and/or activity of the nucleic acids and or polypeptides of the present invention, further fractionation of the positive lead extract is necessary to isolate chemical constituents responsible for the observed effect. Thus, the goal of the extraction, fractionation, and purification process is the careful characterization and
25 identification of a chemical entity within the crude extract having an activity that stimulates or inhibits nucleic acid expression, polypeptide expression, or polypeptide biological activity. The same assays described herein for the detection of activities in mixtures of compounds can be used to purify the active component and to test derivatives thereof. Methods of fractionation and purification of such heterogenous
30 extracts are known in the art. If desired, compounds shown to be useful agents for treatment are chemically modified according to methods known in the art. Compounds identified as being of therapeutic value may be subsequently analyzed

using animal models for diseases in which it is desirable to alter the activity or expression of the nucleic acids or polypeptides of the present invention.

In one embodiment, to identify candidate compounds that alter the biological activity, for example, the enzymatic activity or transcriptional repression activity of
5 an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, a cell, tissue, cell lysate, tissue lysate, or solution containing or expressing an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide (*e.g.*, SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SE
10 ID NO: 8, SEQ ID NO: 10, or another variant encoded by *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)*), or a fragment or derivative thereof (as described above), can be contacted with a candidate compound to be tested under conditions suitable for enzymatic reaction or transcriptional repression reaction, as described herein.

Alternatively, the polypeptide can be contacted directly with the candidate
15 compound to be tested. The level (amount) of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) biological activity is assessed (*e.g.*, the level (amount) of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) biological activity is measured, either directly or indirectly), and is compared with the level of biological activity in a control (*i.e.*, the level of activity
20 of the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide or active fragment or derivative thereof in the absence of the candidate compound to be tested, or in the presence of the candidate compound vehicle only). If the level of the biological activity in the presence of the candidate compound differs, by an amount that is statistically significant, from the level of the biological
25 activity in the absence of the candidate compound, or in the presence of the candidate compound vehicle only, then the candidate compound is a compound that alters the biological activity of an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide. For example, an increase in the level of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS)
30 enzymatic or transcriptional repression activity relative to a control, indicates that the candidate compound is a compound that enhances (is an agonist of) HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) activity. Similarly,

- a decrease in the enzymatic level or transcriptional repression level of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) activity relative to a control, indicates that the candidate compound is a compound that inhibits (is an antagonist of) HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or
- 5 HDRP(Δ NLS) activity. In another embodiment, the level of biological activity of an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide or derivative or fragment thereof in the presence of the candidate compound to be tested, is compared with a control level that has previously been established. A level of the biological activity in the presence of the candidate
- 10 compound that differs from the control level by an amount that is statistically significant indicates that the compound alters HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) biological activity.

- The present invention also relates to an assay for identifying compounds that alter the expression of an *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or
- 15 *HDRP(Δ NLS)* nucleic acid molecule (*e.g.*, antisense nucleic acids, fusion proteins, polypeptides, peptidomimetics, prodrugs, receptors, binding agents, antibodies, small molecules or other drugs, or ribozymes) that alter (*e.g.*, increase or decrease) expression (*e.g.*, transcription or translation) of the nucleic acid molecule or that otherwise interact with the nucleic acids described herein, as well as compounds
- 20 identifiable by the assays. For example, a solution containing a nucleic acid encoding an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide can be contacted with a candidate compound to be tested. The solution can comprise, for example, cells containing the nucleic acid or cell lysate containing the nucleic acid; alternatively, the solution can be another solution
- 25 that comprises elements necessary for transcription/translation of the nucleic acid. Cells not suspended in solution can also be employed, if desired. The level and/or pattern of *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* expression (*e.g.*, the level and/or pattern of mRNA or of protein expressed, such as the level and/or pattern of different variants) is assessed, and is compared with the
- 30 level and/or pattern of expression in a control (*i.e.*, the level and/or pattern of *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* expression in the absence of the candidate compound, or in the presence of the candidate

compound vehicle only). If the level and/or pattern in the presence of the candidate compound differs, by an amount or in a manner that is statistically significant, from the level and/or pattern in the absence of the candidate compound, or in the presence of the candidate compound vehicle only, then the candidate compound is a

5 compound that alters the expression of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. Enhancement of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* expression indicates that the candidate compound is an agonist of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* activity. Similarly, inhibition of *HDAC9*,

10 *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* expression indicates that the candidate compound is an antagonist of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* activity. In another embodiment, the level and/or pattern of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide(s) (e.g., different variants) in the presence of the

15 candidate compound to be tested, is compared with a control level and/or pattern that has previously been established. A level and/or pattern in the presence of the candidate compound that differs from the control level and/or pattern by an amount or in a manner that is statistically significant indicates that the candidate compound alters *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*

20 expression.

In another embodiment of the invention, compounds that alter the expression of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule or that otherwise interact with the nucleic acids described herein, can be identified using a cell, cell lysate, or solution containing a nucleic

25 acid encoding the promoter region of the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* gene operably linked to a reporter gene. After contact with a candidate compound to be tested, the level of expression of the reporter gene (e.g., the level of mRNA or of protein expressed) is assessed, and is compared with the level of expression in a control (i.e., the level of the expression

30 of the reporter gene in the absence of the candidate compound, or in the presence of the candidate compound vehicle only). If the level in the presence of the candidate compound differs, by an amount or in a manner that is statistically significant, from

the level in the absence of the candidate compound, or in the presence of the candidate compound vehicle only, then the candidate compound is a compound that alters the expression of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, as indicated by its ability to alter expression of a gene that is

5 operably linked to the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* gene promoter. Enhancement of the expression of the reporter indicates that the compound is an agonist of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* activity. Similarly, inhibition of the expression of the reporter indicates that the compound is an antagonist of *HDAC9*, *HDAC9a*,

10 *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* activity. In another embodiment, the level of expression of the reporter in the presence of the candidate compound to be tested, is compared with a control level that has previously been established. A level in the presence of the candidate compound that differs from the control level by an amount or in a manner that is statistically significant indicates

15 that the candidate compound alters *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* expression.

Compounds that alter the amounts of different variants encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* (e.g., a compound that enhances activity of a first variant, and that inhibits activity of a second variant),

20 as well as compounds that are agonists of activity of a first variant and antagonists of activity of a second variant, can easily be identified using these methods described above.

In other embodiments of the invention, assays can be used to assess the impact of a candidate compound on the activity of a polypeptide in relation to an

25 *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* substrate, for example, an inhibitor of histone deacetylase activity. These inhibitors fall into four general classes: 1) short-chain fatty acids (e.g., 4-phenylbutyrate and valproic acid); 2) hydroxamic acids (e.g., SAHA, Pyroxamide, trichostatin A (TSA), oxamflatin and CHAPs, such as, CHAP1 and CHAP 31); 3) cyclic tetrapeptides

30 (Trapoxin A, Apicidin and Depsiptide (FK-228, also known as FR9011228); 4) benzamides (e.g., MS-275); and other compounds such as Scriptaid. Examples of such assays and compounds can be found in U.S. Patent Nos. 5,369,108, issued on

November 29, 1994, 5,700,811, issued on December 23, 1997, and 5,773,474, issued on June 30, 1998 to Breslow *et al.*, U.S. Patent Nos. 5,055,608, issued on October 8, 1991, and 5,175,191, issued on December 29, 1992 to Marks *et al.*, as well as, Yoshida *et al.*, *supra*; Saito *et al.*, *supra*; Furamai *et al.*, *supra*; Komatsu *et al.*, *supra*; Su *et al.*, *supra*; Lee *et al.*, *supra* and Suzuki *et al.* *supra*, the entire content of all of which are hereby incorporated by reference.

In one example, a cell or tissue that expresses or contains a compound that interacts with HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) (herein referred to as an "HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) substrate," which can be a polypeptide or other molecule that interacts with HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS)) is contacted with HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) in the presence of a candidate compound, and the ability of the candidate compound to alter the interaction between HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) and the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP (Δ NLS) substrate is determined, for example, by assaying activity of the polypeptide. Alternatively, a cell lysate or a solution containing the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) substrate, can be used. A compound that binds to HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) or the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) substrate can alter the interaction by interfering with, or enhancing the ability of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) to bind to, associate with, or otherwise interact with the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) substrate.

Determining the ability of the candidate compound to bind to HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) or an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) substrate can be accomplished, for example, by coupling the candidate compound with a radioisotope or enzymatic label such that binding of the candidate compound to the polypeptide can be determined by detecting the labeled with ^{125}I , ^{35}S , ^{14}C , or ^3H , either directly or indirectly, and the radioisotope detected by direct counting of

radioemmission or by scintillation counting. Alternatively, candidate compound can be enzymatically labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

5 It is also within the scope of this invention to determine the ability of a candidate compound to interact with the polypeptide without the labeling of any of the interactants. For example, a microphysiometer can be used to detect the interaction of a candidate compound with HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) or an HDAC9, HDAC9a, HDAC9(Δ NLS),
10 HDAC9a(Δ NLS), or HDRP(Δ NLS) substrate without the labeling of either the candidate compound, HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS), or the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) substrate (McConnell *et al.*, (1992) Science, 257: 1906-1912). As used herein, a "microphysiometer" (*e.g.*, CYTOSENSOR™) is an analytical
15 instrument that measures the rate at which a cell acidifies its environment using a light-addressable potentiometric sensor (LAPS). Changes in this acidification rate can be used as an indicator of the interaction between ligand and polypeptide.

 In another embodiment of the invention, assays can be used to identify polypeptides that interact with one or more HDAC9, HDAC9a, HDAC9(Δ NLS),
20 HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptides, as described herein. For example, a yeast two-hybrid system such as that described by Fields and Song (Fields and Song, Nature 340: 245-246 (1989)) can be used to identify polypeptides that interact with one or more HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptides. In such a yeast two-hybrid system, vectors are
25 constructed based on the flexibility of a transcription factor that has two functional domains (a DNA binding domain and a transcription activation domain). If the two domains are separated but fused to two different proteins that interact with one another, transcriptional activation can be achieved, and transcription of specific markers (*e.g.*, nutritional markers such as His and Ade, or color markers such as
30 lacZ) can be used to identify the presence of interaction and transcriptional activation. For example, in the methods of the invention, a first vector is used that includes a nucleic acid encoding a DNA binding domain and an HDAC9, HDAC9a,

HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, variant, or fragment or derivative thereof, and a second vector is used that includes a nucleic acid encoding a transcription activation domain and a nucleic acid encoding a polypeptide that potentially may interact with the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, variant, or fragment or derivative thereof (e.g., an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide substrate or receptor). Incubation of yeast containing the first vector and the second vector under appropriate conditions (e.g., mating conditions such as used in the MATCHMAKER™ system from Clontech) allows identification of colonies that express the markers of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS). These colonies can be examined to identify the polypeptide(s) that interact with the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide or fragment or derivative thereof. Such polypeptides may be useful as compounds that alter the activity or expression of an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, as described above.

In more than one embodiment of the above assay methods of the present invention, it may be desirable to immobilize an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, or an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) substrate, or other components of the assay on a solid support, in order to facilitate separation of complexed from uncomplexed forms of one or both of the polypeptides, as well as to accommodate automation of the assay. Binding of a candidate compound to the polypeptide, or interaction of the polypeptide with a substrate in the presence and absence of a candidate compound, can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtitre plates, test tubes, and micro-centrifuge tubes. In one embodiment, a fusion protein (e.g., a glutathione-S-transferase fusion protein) can be provided that adds a domain that allows HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) or an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) substrate to be bound to a matrix or other solid support.

In another embodiment, modulators of expression of nucleic acid molecules of the invention are identified in a method wherein a cell, cell lysate, tissue, tissue lysate, or solution containing a nucleic acid encoding HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) is contacted with a candidate compound and the expression of appropriate mRNA or polypeptide (*e.g.*, variant(s)) in the cell, cell lysate, tissue, or tissue lysate, or solution, is determined. The level of expression of appropriate mRNA or polypeptide(s) in the presence of the candidate compound is compared to the level of expression of mRNA or polypeptide(s) in the absence of the candidate compound, or in the presence of the candidate compound vehicle only. The candidate compound can then be identified as a modulator of expression based on this comparison. For example, when expression of mRNA or polypeptide is greater (statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator or enhancer of the mRNA or polypeptide expression. Alternatively, when expression of the mRNA or polypeptide is less (statistically significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of the mRNA or polypeptide expression. The level of mRNA or polypeptide expression in the cells can be determined by methods described herein for detecting mRNA or polypeptide.

This invention further pertains to novel compounds identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further use a compound identified as described herein in an appropriate animal model. For example, a compound identified as described herein (*e.g.*, a candidate compound that is a modulating compound such as an antisense nucleic acid molecule, a specific antibody, or a polypeptide substrate) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such a compound. Alternatively, a compound identified as described herein can be used in an animal model to determine the mechanism of action of such a compound. Furthermore, this invention pertains to uses of novel compounds identified by the above-described screening assays for treatments as described herein. In addition, a compound identified as described herein can be used to alter activity of an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, or to

alter expression of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, by contacting the polypeptide or the nucleic acid molecule (or contacting a cell comprising the polypeptide or the nucleic acid molecule) with the compound identified as described herein.

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PHARMACEUTICAL COMPOSITIONS

The present invention also pertains to pharmaceutical compositions comprising nucleic acids described herein, particularly nucleotides encoding the polypeptides described herein; comprising polypeptides described herein (*e.g.*, SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, and/or other variants encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*); and/or comprising a compound that alters (*e.g.*, increases or decreases) *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* expression or *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide activity as described herein. For instance, a polypeptide, protein, fragment, fusion protein or prodrug thereof, or a nucleotide or nucleic acid construct (vector) comprising a nucleotide of the present invention, a compound that alters *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide activity, a compound that alters *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid expression, or an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* substrate or binding partner, can be formulated with a physiologically acceptable carrier or excipient to prepare a pharmaceutical composition. The carrier and composition can be sterile. The formulation should suit the mode of administration.

Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions (*e.g.*, NaCl), saline, buffered saline, alcohols, glycerol, ethanol, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose, amylose or starch, dextrose, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrrolidone, etc., as well as combinations thereof. The pharmaceutical preparations can, if desired, be mixed with auxiliary agents, *e.g.*, lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic

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pressure, buffers, coloring, flavoring and/or aromatic substances and the like that do not deleteriously react with the active compounds.

The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. The composition can be a liquid
5 solution, suspension, emulsion, tablet, pill, capsule, sustained release formulation, or powder. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, polyvinyl pyrrolidone, sodium saccharine, cellulose, magnesium carbonate,
10 etc.

Methods of introduction of these compositions include, but are not limited to, intradermal, intramuscular, intraperitoneal, intraocular, intravenous, subcutaneous, topical, oral and intranasal. Other suitable methods of introduction can also include gene therapy (as described below), rechargeable or biodegradable
15 devices, particle acceleration devices ("gene guns") and slow release polymeric devices. The pharmaceutical compositions of this invention can also be administered as part of a combinatorial therapy with other compounds.

The composition can be formulated in accordance with the routine procedures as a pharmaceutical composition adapted for administration to human
20 beings. For example, compositions for intravenous administration typically are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free
25 concentrate in a hermetically sealed container such as an ampule or sachette indicating the quantity of active compound. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water, saline or dextrose/water. Where the composition is administered by injection, an ampule of sterile water for injection or saline can be
30 provided so that the ingredients may be mixed prior to administration.

For topical application, nonsprayable forms, viscous to semi-solid or solid forms comprising a carrier compatible with topical application and having a

dynamic viscosity preferably greater than water, can be employed. Suitable formulations include but are not limited to solutions, suspensions, emulsions, creams, ointments, powders, enemas, lotions, sols, liniments, salves, aerosols, etc., that are, if desired, sterilized or mixed with auxiliary agents, *e.g.*, preservatives, stabilizers, wetting agents, buffers or salts for influencing osmotic pressure, etc. The compound may be incorporated into a cosmetic formulation. For topical application, also suitable are sprayable aerosol preparations wherein the active ingredient, preferably in combination with a solid or liquid inert carrier material, is packaged in a squeeze bottle or in admixture with a pressurized volatile, normally gaseous propellant, *e.g.*, pressurized air.

Compounds described herein can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with free amino groups such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with free carboxyl groups such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

The compounds are administered in a therapeutically effective amount. The amount of compounds that will be therapeutically effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the symptoms of a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, and should be decided according to the judgment of a practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, that notice

reflects approval by the agency of manufacture, use of sale for human administration. The pack or kit can be labeled with information regarding mode of administration, sequence of drug administration (*e.g.*, separately, sequentially or concurrently), or the like. The pack or kit may also include means for reminding the
5 patient to take the therapy. The pack or kit can be a single unit dosage of the combination therapy or it can be a plurality of unit dosages. In particular, the compounds can be separated, mixed together in any combination, present in a single vial or tablet. Compounds assembled in a blister pack or other dispensing means is preferred. For the purpose of this invention, unit dosage is intended to mean a
10 dosage that is dependent on the individual pharmacodynamics of each compound and administered in FDA approved dosages in standard time courses.

METHODS OF THERAPY

The present invention also pertains to methods of treatment (prophylactic,
15 diagnostic, and/or therapeutic) for a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, using an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) therapeutic compound. An "HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) therapeutic compound" is a compound that alters (*e.g.*, enhances or inhibits) HDAC9, HDAC9a,
20 HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide activity and/or *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* nucleic acid molecule expression, as described herein (*e.g.*, an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) agonist or antagonist).
HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS)
25 therapeutic compounds can alter HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide activity or nucleic acid molecule expression by a variety of means, such as, for example, by providing additional HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide or by upregulating the transcription or translation of the *HDAC9*,
30 *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* nucleic acid molecule; by altering post-translational processing of the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide; by altering

transcription of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* variants; or by interfering with *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide activity (*e.g.*, by binding to an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide), or by downregulating the transcription or translation of the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule. Representative *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* therapeutic compounds include the following: nucleic acids or fragments or derivatives thereof described herein, particularly nucleotides encoding the polypeptides described herein and vectors comprising such nucleic acids (*e.g.*, a nucleic acid molecule, cDNA, and/or RNA, such as a nucleic acid encoding an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide or active fragment or derivative thereof, or an oligonucleotide; for example, SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9, which may optionally comprise at least one polymorphism, or a nucleic acid encoding SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, or fragments or derivatives thereof); polypeptides described herein (*e.g.*, SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10 and/or other variants encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, or fragments or derivatives thereof); *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* substrates; peptidomimetics; fusion proteins or prodrugs thereof; antibodies (*e.g.*, an antibody to a mutant *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide, or an antibody to a non-mutant *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide, or an antibody to a particular variant encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, as described above); ribozymes; other small molecules; and other compounds that alter (*e.g.*, enhance or inhibit) *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid expression or polypeptide activity, for example, those compounds identified in the screening methods described herein, or that regulate transcription of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* variants (*e.g.*,

compounds that affect which variants are expressed, or that affect the amount of each variant that is expressed. More than one HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) therapeutic compound can be used concurrently, if desired.

- 5 The HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) therapeutic compound that is a nucleic acid is used in the treatment of a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. The term, "treatment" as used herein, refers not only to ameliorating symptoms associated with the disease, but also preventing or delaying the onset of the disease,
- 10 and also lessening the severity or frequency of symptoms of the disease. The therapy is designed to alter (*e.g.*, inhibit or enhance), replace or supplement activity of an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide in an individual. For example, an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) therapeutic compound can be administered in
- 15 order to upregulate or increase the expression or availability of the *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* nucleic acid molecule or of specific variants of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS), or, conversely, to downregulate or decrease the expression or availability of the *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or
- 20 *HDRP(Δ NLS)* nucleic acid molecule or specific variants of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS). Upregulation or increasing expression or availability of a native *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* nucleic acid molecule or of a particular variant could interfere with or compensate for the expression or activity of a defective gene
- 25 or another variant; downregulation or decreasing expression or availability of a native *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* nucleic acid molecule or of a particular variant could minimize the expression or activity of a defective gene or the particular variant and thereby minimize the impact of the defective gene or the particular variant.
- 30 The HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) therapeutic compound(s) are administered in a therapeutically effective amount (*i.e.*, an amount that is sufficient to treat the disease, such as by

ameliorating symptoms associated with the disease, preventing or delaying the onset of the disease, and/or also lessening the severity or frequency of symptoms of the disease). The amount that will be therapeutically effective in the treatment of a particular individual's disorder or condition will depend on the symptoms and
5 severity of the disease, and can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of a practitioner and each
10 patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

In one embodiment, a nucleic acid of the invention (*e.g.*, a nucleic acid encoding an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, such as SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5,
15 SEQ ID NO: 7, or SEQ ID NO: 9, which may optionally comprise at least one polymorphism, or a nucleic acid that encodes an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide or a variant, derivative or fragment thereof, such as a nucleic acid encoding the protein of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10) can
20 be used, either alone or in a pharmaceutical composition as described above. For example, *HDAC9*, *HDAC9a*, *HDAC9*(Δ NLS), *HDAC9a*(Δ NLS), or *HDRP*(Δ NLS) or a cDNA encoding an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, either by itself or included within a vector, can be introduced into cells (either *in vitro* or *in vivo*) such that the cells produce native
25 HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide. If desired, cells that have been transformed with the gene or cDNA or a vector comprising the gene or cDNA can be introduced (or re-introduced) into an individual affected with the disease. Thus, cells that, in nature, lack native *HDAC9*, *HDAC9a*, *HDAC9*(Δ NLS), *HDAC9a*(Δ NLS), or *HDRP*(Δ NLS) expression and
30 activity, or have mutant *HDAC9*, *HDAC9a*, *HDAC9*(Δ NLS), *HDAC9a*(Δ NLS), or *HDRP*(Δ NLS) expression and activity, or have expression of a disease-associated HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) variant,

can be engineered to express an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide or an active fragment of an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide (or a different variant of an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide). In a preferred embodiment, nucleic acid encoding the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, or an active fragment or derivative thereof, can be introduced into an expression vector, such as a viral vector, and the vector can be introduced into appropriate cells in an animal. Other gene transfer systems, including viral and nonviral transfer systems, can be used. Alternatively, nonviral gene transfer methods, such as calcium phosphate coprecipitation, mechanical techniques (e.g., microinjection); membrane fusion-mediated transfer via liposomes; or direct DNA uptake, can also be used to introduce the desired nucleic acid molecule into a cell.

Alternatively, in another embodiment of the invention, a nucleic acid of the invention; a nucleic acid complementary to a nucleic acid of the invention; or a portion of such a nucleic acid (e.g., an oligonucleotide as described below), can be used in "antisense" therapy, in which a nucleic acid (e.g., an oligonucleotide) that specifically hybridizes to the RNA and/or genomic DNA of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) is administered or generated *in situ*. The antisense nucleic acid that specifically hybridizes to the RNA and/or DNA inhibits expression of the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) nucleic acid molecule, e.g., by inhibiting translation and/or transcription. Binding of the antisense nucleic acid can be by conventional base pair complementarity, or, for example, in the case of binding to DNA duplexes, through specific interaction in the major groove of the double helix.

An antisense construct of the present invention can be delivered, for example, as an expression plasmid as described above. When the plasmid is transcribed in the cell, it produces RNA that is complementary to a portion of the mRNA and/or DNA that encodes an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide. Alternatively, the antisense construct can be an oligonucleotide probe which is generated *ex vivo* and introduced

into cells; it then inhibits expression by hybridizing with the mRNA and/or genomic DNA of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. In one embodiment, the oligonucleotide probes are modified oligonucleotides that are resistant to endogenous nucleases, *e.g.* exonucleases and/or endonucleases, thereby rendering them stable *in vivo*. Exemplary nucleic acid molecules for use as antisense oligonucleotides are phosphoramidate, phosphothioate and methylphosphonate analogs of DNA (see also U.S. Patent Nos. 5,176,996; 5,264,564; and 5,256,775). Additionally, general approaches to constructing oligomers useful in antisense therapy are also described, for example, by Van der Krol *et al.*, *Biotechniques* 6: 958-976 (1988); and Stein *et al.*, *Cancer Res* 48: 2659-2668 (1988). With respect to antisense DNA, oligodeoxyribonucleotides derived from the translation initiation site, *e.g.* between the -10 and +10 regions of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid sequence, are preferred.

To perform antisense therapy, oligonucleotides (RNA, cDNA or DNA) are designed that are complementary to mRNA encoding an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide. The antisense oligonucleotides bind to *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* mRNA transcripts and prevent translation. Absolute complementarity, although preferred, is not required. A sequence "complementary" to a portion of an RNA, as referred to herein, indicates that a sequence has sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double-stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid, as described in detail above. Generally, the longer the hybridizing nucleic acid, the more base mismatches with an RNA it may contain and still form a stable duplex (or triplex, as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures.

The oligonucleotides used in antisense therapy can be DNA, RNA, or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotides can be modified at the base moiety, sugar

moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotides can include other appended groups such as peptides (*e.g.* for targeting host cell receptors *in vivo*), or compounds facilitating transport across the cell membrane (see, *e.g.*, Letsinger *et al.*, Proc. Natl. Acad. Sci. USA 86: 6553-6556 (1989); Lemaitre *et al.*, Proc. Natl. Acad. Sci. USA 84: 648-652 (1987); PCT International Publication No. W088/09810)) or the blood-brain barrier (see, *e.g.*, PCT International Publication No. W089/10134), or hybridization-triggered cleavage agents (see, *e.g.*, Krol *et al.*, BioTechniques 6: 958-976 (1988)) or intercalating agents. (See, *e.g.*, Zon, Pharm. Res. 5: 539-549 (1988)). To this end, the oligonucleotide may be conjugated to another molecule (*e.g.*, a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent).

The antisense molecules are delivered to cells that express *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* *in vivo*. A number of methods can be used for delivering antisense DNA or RNA to cells; *e.g.*, antisense molecules can be injected directly into the tissue site, or modified antisense molecules, designed to target the desired cells (*e.g.*, antisense linked to peptides or antibodies that specifically bind receptors or antigens expressed on the target cell surface) can be administered systematically. Alternatively, in a preferred embodiment, a recombinant DNA construct is utilized in which the antisense oligonucleotide is placed under the control of a strong promoter (*e.g.*, pol III or pol II). The use of such a construct to transfect target cells in the patient results in the transcription of sufficient amounts of single stranded RNAs that will form complementary base pairs with the endogenous *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* transcripts and thereby prevent translation of the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* mRNA. For example, a vector can be introduced *in vivo* such that it is taken up by a cell and directs the transcription of an antisense RNA. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art and described above. For example, a plasmid, cosmid, YAC, or viral vector can be used to prepare the recombinant DNA

construct that can be introduced directly into the tissue site. Alternatively, viral vectors can be used that selectively infect the desired tissue, in which case administration may be accomplished by another route (*e.g.*, systematically).

- Endogenous *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or
- 5 *HDRP(ΔNLS)* expression can also be reduced by inactivating or “knocking out” *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid sequences or their promoters using targeted homologous recombination (*e.g.*, see Smithies *et al.*, Nature 317: 230-234 (1985); Thomas and Capecchi, Cell 51: 503-512 (1987); Thompson *et al.*, Cell 5: 313-321 (1989)). For example, a mutant,
- 10 non-functional *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* (either the coding regions or regulatory regions of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*) can be
- 15 used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* *in vivo*. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. The recombinant DNA constructs can be
- 20 directly administered or targeted to the required site *in vivo* using appropriate vectors, as described above. Alternatively, expression of non-mutant *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* can be increased using a similar method: Targeted homologous recombination can be used to insert a DNA construct comprising a non-mutant, functional *HDAC9*, *HDAC9a*,
- 25 *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* (*e.g.*, a gene having SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9, which may optionally comprise at least one polymorphism), or a portion thereof, in place of a mutant *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* in the cell, as described above. In another embodiment, targeted homologous
- 30 recombination can be used to insert a DNA construct comprising a nucleic acid that encodes an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide variant that differs from that present in the cell.

Alternatively, endogenous *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* expression can be reduced by targeting deoxyribonucleotide sequences complementary to the regulatory region of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* (i.e., the *HDAC9*,
5 *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* promoter and/or enhancers) to form triple helical structures that prevent transcription of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* in target cells in the body. (See generally, Helene Anticancer Drug Des., 6(6): 569-84 (1991); Helene *et al.*, Ann. N.Y. Acad. Sci., 660: 27-36 (1992); and Maher, Bioassays 14(12): 807-15
10 (1992)). Likewise, the antisense constructs described herein, by antagonizing the normal biological activity of one of the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* proteins, can be used in the manipulation of tissue, e.g., tissue differentiation, both *in vivo* and for *ex vivo* tissue cultures. Furthermore, the antisense techniques (e.g., microinjection of antisense molecules,
15 or transfection with plasmids whose transcripts are anti-sense with regard to an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* mRNA or gene sequence) can be used to investigate role of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* in developmental events, as well as the normal cellular function of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*,
20 *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* in adult tissue. Such techniques can be utilized in cell culture, but can also be used in the creation of transgenic animals.

In yet another embodiment of the invention, other *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* therapeutic compounds as described herein can also be used in the treatment or prevention of a cell
25 proliferation disease, an apoptotic disease, or a cell differentiation disease. The therapeutic compounds can be delivered in a composition, as described above, or by themselves. They can be administered systemically, or can be targeted to a particular tissue. The therapeutic compounds can be produced by a variety of means, including chemical synthesis; recombinant production; *in vivo* production
30 (e.g., a transgenic animal, such as U.S. Patent No. 4,873,316 to Meade *et al.*), for example, and can be isolated using standard means such as those described herein.

A combination of any of the above methods of treatment (e.g., administration of non-mutant HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide in conjunction with antisense therapy targeting mutant *HDAC9*, *HDAC9a*, *HDAC9*(Δ NLS), *HDAC9a*(Δ NLS), or
5 *HDRP*(Δ NLS) mRNA; administration of a first variant encoded by *HDAC9*, *HDAC9a*, *HDAC9*(Δ NLS), *HDAC9a*(Δ NLS), or *HDRP*(Δ NLS) in conjunction with antisense therapy targeting a second encoded by *HDAC9*, *HDAC9a*, *HDAC9*(Δ NLS), *HDAC9a*(Δ NLS), or *HDRP*(Δ NLS), can also be used.

In another embodiment, the invention is directed to *HDAC9*, *HDAC9a*,
10 *HDAC9*(Δ NLS), *HDAC9a*(Δ NLS), or *HDRP*(Δ NLS) nucleic acid molecules and *HDAC9*, *HDAC9a*, *HDAC9*(Δ NLS), *HDAC9a*(Δ NLS), or *HDRP*(Δ NLS) polypeptides for use as a medicament in therapy. For example, the nucleic acid molecules or polypeptides of the present invention can be used in the treatment of a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. In
15 addition, the *HDAC9*, *HDAC9a*, *HDAC9*(Δ NLS), *HDAC9a*(Δ NLS), or *HDRP*(Δ NLS) nucleic acid molecules and *HDAC9*, *HDAC9a*, *HDAC9*(Δ NLS), *HDAC9a*(Δ NLS), or *HDRP*(Δ NLS) polypeptides described herein can be used in the manufacture of a medicament for the treatment of a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

20 The invention will be further described by the following non-limiting examples. The teachings of all publications cited herein are incorporated herein by reference in their entirety.

EXEMPLIFICATION

25 *Cloning of cDNA encodes a novel HDAC, designated HDAC9*

HDAC9 was cloned by PCR and 3' rapid amplification of cDNA ends using primers designed from the sequence of human chromosome 7 whose translated product exhibited 80% identity to the HDAC domain of HDAC4, described in detail as follows.

30 Database analyses indicate that *HDRP* is located on chromosome 7 (7p15-p21). The human genome database (February 2001 release) of GenBank was searched using the human HDAC4 amino acid sequence. The TBLASTN program

was used to identify open reading frames downstream of *HDRP* on chromosome 7 that exhibit significant homology to the HDAC domain of HDAC4. Several fragments whose translated products exhibit over 58% identity were retrieved. Two sense primers (OL486, 5'-CCATGGAAACGGTACCCAGCAGGC-3' (SEQ ID NO: 16) and OL487, 5'-CACTCCATCGCTATGATGAAGGG-3' (SEQ ID NO: 17)) and antisense primers (OL484, 5'-AGTTCCTTCATCATAGCGATGG-3' (SEQ ID NO: 18) and OL485, 5'-AATGTACAGGATGCTGGGGT-3' (SEQ ID NO: 19)) each were designed based upon one of these fragments whose translated products matched amino acids 842-873 of HDAC4. RT-PCR was performed using each of the antisense primers and a sense primer (5'-CCCTTGCTAGCTGGTGGAGTTCCCTT-3' (SEQ ID NO: 20)) from the coding region of *HDRP* and human brain cDNA as a template. PCR was performed in a Biometra TGRADIENT Thermocycler for 30 cycles at 95°C for 20 seconds, 60°C for 20 seconds, and 72°C for 120 seconds.

3'-rapid amplification of cDNA ends was performed using the sense primer OL486 and adaptor primer 1 (Clontech), and marathon-ready cDNA from human brain (Clontech, Palo Alto, CA) according to the manufacturer's instruction. The products were re-amplified using nested sense primer OL487 and adaptor primer 2 (Clontech, Palo Alto, CA). PCR products were cloned into pGEM-T-easy vector (Promega, Madison, WI) and sequenced using an automated DNA sequencer at the DNA Sequencing Core Facility of the Memorial Sloan-Kettering Cancer Center, using DNA sequencing methods known to one of skill in the art.

Two cDNAs were cloned from the above-described methods. One cDNA (SEQ ID NO:1) encodes an HDAC9 protein that is 1011 amino acids in length. The other cDNA (SEQ ID NO: 3) encodes an HDAC9a protein that is 879 amino acids long. The cDNA sequence and amino sequence of *HDAC9* and *HDAC9a* are shown in FIGS. 1A-1G and FIGS. 2A-2B, respectively. Database analyses of these cDNAs against human genomic DNA sequences indicated that these two cDNAs are generated by alternatively splicing. An alignment of HDAC9, HDAC9a, HDRP, and HDAC4 is shown in FIGS. 3A-3C.

Each of the HDAC9 and HDAC9a nucleic acid sequences were cloned into the pFLAG-CMV-5b vector (Sigma) in frame with the C-terminal FLAG tag. Only

the coding regions plus three extra base pairs (ACC) of cDNA of the HDAC9 and HDAC9a nucleic acid sequences were included in the constructs. These constructs are referred to herein as HDAC9-FLAG and HDAC9a-FLAG, respectively. These constructs are contained in *E. coli*, and can readily be expressed. For HDAC9, the
5 insert is 3033 bp and for HDAC9a, the insert size is 2637 bp. Both HDAC9 and HDAC9a can be released with EcoRV and BamHI (whose sites have been incorporated in the primers to obtain HDAC9 and HDAC9a coding cDNA for cloning purpose) restriction enzyme digestion.

The *HDAC9* cDNA sequences from the known 5'-end of *HDRP* cDNA to the
10 3'-untranslated region cloned in this study cover over 511 kb of genomic DNA on chromosome 7. As shown in FIG. 4, the coding region cDNA of *HDAC9* resides in 23 exons spanning 458 kb of genomic sequence. Exons 21, 22, and 23 are one single exon in HDAC9a, but the middle exon that is numbered exon 22 in FIG. 4, containing an in-frame stop codon, is spliced out in HDAC9. In addition, exons 12
15 and 13 are a single exon used by HDRP. Exon 13 is spliced as part of an intron in HDAC9 and HDAC9a.

Further analysis revealed that exon 7, which contains a nuclear localization signal (NLS) is alternatively spliced in an HDRP isoform, creating HDRP(Δ NLS). RT-PCR analyses using primers based on sequences from exon 6 and exon 14
20 indicate that this alternative splicing event also occurs in *HDAC9* and/or *HDAC9a*. Thus, it is possible that at least 6 proteins can be generated from a single *HDAC9* gene by alternatively splicing of its RNA. The cDNA sequences and amino acid sequences for HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), and HDRP(Δ NLS) are shown in FIGS. 1A-1O and 2A-2E, respectively.

25

HDAC9 mRNA is differentially expressed among human tissues

The expression of *HDAC9* mRNA was determined by Northern blot analysis using a human multiple tissue Northern blot (Clontech, Palo Alto, CA). Hybridization was performed according to the manufacturer's instruction using
30 ExPressHyb solution (Clontech, Palo Alto, CA). The 32 P-random priming labeled 3'-untranslated region common to both *HDAC9* and *HDAC9a* that shares no significant sequence homology with *HDRP* was used as a probe. Two transcripts at

9.8 and 4.1 kb were detected in all tissues examined (FIG. 6A). The 4.1 kb transcript is shorter than the 4.4 kb *HDRP* transcript (See Zhou, *et al.*, Proc. Natl. Acad. Sci. USA, 97:1056-1061 (2000)). A third transcript at 1.2 kb was detected in placenta (FIG. 6A). Similar to *HDRP* (See Zhou, X., *et al.*, Proc. Natl. Acad. Sci. USA, 97:1056-1061 (2000)), high levels of *HDAC9* transcripts were detected in brain and skeletal muscle (FIG. 6A).

The distribution of alternatively spliced mRNA variants among tissues was examined by RT-PCR using primers (OL516 5'-TGTGTCATCGAGCTGGCTTC-3' (SEQ ID NO: 21) and OL517 5'-ATCTTCTGCAAGTGGCTCCA-3' (SEQ ID NO: 22)) spanning the alternatively spliced exon 22 and cDNA panel from the same tissues as the multiple tissue Northern blot. PCR was performed in a Biometra TGRADIENT Thermocycler for 30 cycles at 95°C for 20 seconds, 60°C for 20 seconds, and 72°C for 60 seconds. The expected sizes of PCR products were 680 base pairs for *HDAC9* and 993 base pairs for *HDAC9a*. The ratio of *HDAC9* and *HDAC9a* transcripts differed among tissues (FIG. 6B). In the placenta and kidney, the levels of the two transcripts were about the same (FIG. 6B). In the brain, heart, and pancreas, there were more transcripts of *HDAC9* than *HDAC9a*. In the other tissues examined, there were more *HDAC9a* transcripts than *HDAC9* transcripts (FIG. 6B). Under the conditions tested, *HDAC9* transcripts were undetectable in liver (FIG. 6B). The lung had an *HDAC9* product that was larger than expected and abundant. The lung also had low levels of *HDAC9* transcripts and *HDAC9a* transcripts (FIG. 6B). An additional PCR product was also amplified from cDNA of the pancreas; this product was than the expected products from *HDAC9* and *HDAC9a* (FIG. 6B). The identity of the different sized transcripts is unknown.

HDAC9 and HDAC9a possess histone deacetylase activity

HDAC9 was named based on sequence homology to *HDAC4* (FIGS. 3A-3C). To determine whether *HDAC9* and *HDAC9a* possess HDAC activity, an HDAC enzymatic assay was performed using anti-FLAG immunoprecipitated *HDAC9*-FLAG and *HDAC9a*-FLAG.

C-terminal FLAG-tagged *HDAC9* (*HDAC9*-FLAG) and *HDAC9a* (*HDAC9a*-FLAG) expression vectors were constructed using the pFLAG-CMV-5b

vector (Sigma) and PCR amplified coding regions of HDAC9 and HDAC9a in frame with the FLAG-tag to form pFLAG-CMV-5b-HDAC9 (plasmid VR1) and pFLAG-CMV-5b-HDAC9a (plasmid VR2). All constructs were confirmed by DNA sequencing.

- 5 Transfection of human kidney 293T cells, immunoprecipitation using anti-FLAG M2 Agarose (Sigma), Western blot analyses and dual luciferase assays were performed essentially as previously described by Zhou *et al.* (Proc. Natl. Acad. Sci. USA, 97:1056-1061 (2000)). Briefly, the cells (American Type Culture Collection) were cultured in DME HG medium (GIBCO/BRL) supplemented with 10%
10 (vol/vol) FBS at 37 °C in a 5% CO₂ atmosphere. Transient transfection was performed by using Lipofectamine (GIBCO/BRL) or Fugene 6 (Roche Molecular Biochemicals) according to the manufacturers' instructions. Cells were harvested 24 to 48 hours after transfection and lysed in IP lysis buffer (50 mM Tris-HCl, pH 7.5/120 mM NaCl/5 mM EDTA/0.5% NP-40) at 5 x 10⁷ cells per ml.
15 Immunoprecipitation with anti-FLAG M2-agarose (Sigma, St. Louis, MO) was performed according to the manufacturer's instructions. Immunoprecipitated proteins were released from the agarose beads by using FLAG-peptide and either used directly for HDAC enzymatic activity assays or resolved on SDS/PAGE for Western blot analyses. Anti-FLAG antibody was purchased from Sigma (St. Louis,
20 MO). Western blot analyses were performed using standard methods.

- HDAC9 and HDAC9a enzymatic activity were assessed with the HDAC Fluorescent Activity Assay/Drug Discovery Kit-AK-500 (BIOMOL Research Laboratories) using a FLUOR DE LYSTM that contains an acetylated lysine side chain as a substrate and immunoprecipitated HDAC9-FLAG and HDAC9a-FLAG
25 polypeptides according to the manufacturer's instruction and a SPECTRAMax[®] GEMINI XS microplate spectrofluorometer using the SOFTmax[®] PRO system (Molecular Devices) at excitation 355 nm and emission 460 nm with a cut off filter of 455 nm. Briefly, HDAC9-FLAG and HDAC9a-FLAG were incubated with the substrate overnight at room temperature in a 96-well plate. The reaction was
30 stopped by addition of Fluor De LysTM Developer and samples were read with the fluorometer.

As shown in FIG. 7, both HDAC9-FLAG and HDAC9a-FLAG deacetylated the acetylated lysine of FLUOR DE LYSTM and the activity of HDAC9 and HDAC9a was comparable. To examine the activity of HDAC9 and HDAC9a, inhibition studies using TSA were carried out by preincubating HDAC9-FLAG and HDAC9a-FLAG with TSA for 15 minutes at room temperature. The assay was then carried out as stated above. As shown in FIG. 7, TSA inhibited HDAC9 and HDAC9a deacetylase activity. The inset gel in FIG. 7 shows the amount of protein used in the assay. SAHA, a potent HDAC inhibitor (Richon *et al.*, Proc. Natl. Acad. Sci. USA, 95:3003-3007 (1998)) also completely inhibited the histone deacetylase activity of HDAC9-FLAG and HDAC9a-FLAG. The HDAC activity of HDAC9 and HDAC9a was about ten times lower than the deacetylase activity of HDAC4 when comparable amount of protein was used under conditions tested here.

HDAC9 and HDAC9a enzymatic activity was also determined through HDAC enzymatic assays using ³H-histones isolated from murine erythroleukemia cells as a substrate. This assay was performed essentially as described by Richon *et al.* (Proc. Natl. Acad. Sci. USA, 95:3003-3007 (1998)). Briefly, HDAC9-FLAG and HDAC9a-FLAG were incubated with ³H-histones overnight at 37°C. The reaction was stopped by the addition of 1M HCl/0.1 acetic acid. Released ³H-acetic acid was extracted with ethyl acetate and quantified by scintillation counting. For inhibition studies, the immunoprecipitated complexes were preincubated with the different HDAC inhibitors for 30 minutes at 4°C.

As shown in FIG. 8, HDAC9a-FLAG deacetylated ³H-acetyl-histones. SAHA, a potent HDAC inhibitor also completely inhibited the histone deacetylase activity of HDAC9a-FLAG. TSA also inhibited HDAC9a deacetylase activity. Similar results were obtained when HDAC9 was used as the enzyme source.

HDAC9 and HDAC9a repress MEF2-mediated transcription

The Xenopus homolog of HDRP, MITR, was identified as a MEF2 interacting transcriptional repressor (Sparrow *et al.*, EMBO J. 18:5085-5098(1999)) and mouse HDRP also interacts with and represses MEF2 mediated transcription (Zhang *et al.*, J. Biol. Chem. 276:35-39 (2001)). We first tested whether HDAC9-FLAG and HDAC9a-FLAG interact with MEF2. 293 cells were transfected with

vector, HDAC9-FLAG, or HDAC9a-FLAG. The cells were subsequently lysed and HDAC9-FLAG and HDAC9a-FLAG proteins were immunoprecipitated with anti-FLAG antibodies. Western blot analysis of the immunoprecipitated proteins was carried out, using anti-MEF-2 antibody to probe the blot. As shown in FIG. 9A, both HDAC9 and HDAC9a interacted with MEF2 in 293T cells.

It was then determined whether HDAC9 and HDAC9a repress MEF2-mediated transcription. This determination was carried out as follows. The p3XMEF2-luciferase reporter gene (100 ng) and the vector pRL-TK (Promega) (5 ng) were co-transfected into 293T cells in the absence (pcDNA3 empty vector) or presence of MEF2C (100 ng of pCMV-MEF2C). HDAC9-F (1 ng, 10 ng, or 100 ng of pFLAG-HDAC9; pFLAG-HDAC9 and HDAC9-FLAG are different constructs, with the FLAG sequence located at opposite ends of the HDAC9 nucleotide, but are functionally equivalent) or HDAC9a-F (1 ng, 10 ng, or 100 ng of pFLAG-HDAC9a; pFLAG-HDAC9a and HDAC9a-FLAG are different constructs, with the FLAG sequence located at opposite ends of the HDAC9a nucleotide, but are functionally equivalent) was included in a subset of experimental groups with the MEF2C vector. pFLAG empty vector was used to adjust the DNA to an equal amount in each transfection. The cells were harvested 24 to 36 hours after transfection and the luciferase activities were measured using the Dual-Luciferase™ Reporter Assay System from Promega according to the manufacturer's instruction. The firefly luciferase activity was first normalized to the co-transfected Renilla luciferase activity (encoded by the pRL-TK vector), and the luciferase activity value for cells transfected with MEF2C alone was set at 1. MEF2C activated transcription over 30 times the basal level of transcription. As shown in FIG. 9B, HDAC9-FLAG and HDAC9a-FLAG repressed MEF2C mediated transcriptional activation in a dose-dependent manner and completely abolished the activation at the 100 ng dose for both HDAC9 and HDAC9a. The transcriptional repression effect of HDAC9 and HDAC9a on MEF2C mediated transcription was a specific effect since a co-transfected reporter gene for transfection efficiency containing a TK promoter was not repressed by HDAC9 or HDAC9a.

Described herein is the identification and characterization of a new class II HDAC, designated HDAC9. HDAC9 has several alternatively spliced isoforms,

one of which is the previously identified HDRP (Zhou *et al.*, Proc. Natl. Acad. Sci. USA 97:1056-1061 (2000)). HDAC9 and HDAC9a possess HDAC activity, which appears to have a lower specific enzymatic activity than HDAC4. While not wishing to be bound by any particular theory, it is possible that an essential co-factor is lost during immunoprecipitation or does not exist in 293T cells (for example, metastasis-associated protein 2 is essential for the assembly of a catalytically active HDAC1 (Zhang *et al.*, Genes Dev. 13:1924-1935 (1999)), the substrates used are not its natural substrate, or the FLAG tag which interferes with the folding of the protein.

10 Searching the human genome with the HDAC domain from either HDAC1 or HDAC9 identified a total of 10 HDACs in the presently completed human genome sequence, a number of which are schematically represented in FIG. 10. HDACs 1, 2, 3, 8, 4, 5, 6, 7, 9, and 9a all have HDAC domains. HDRP, which is also schematically depicted in FIG. 10, does not have a catalytic domain.

15 All references described herein are incorporated by reference in their entirety. While this invention has been particularly shown and described with reference to preferred embodiment thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the spirit and scope of the invention as defined by the appended
20 claims.

CLAIMS

What is claimed is:

- 5
1. An isolated or recombinant histone deacetylase polypeptide, said polypeptide selected from:
- 10 a) an isolated or recombinant polypeptide comprising SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10; and
- b) an isolated or recombinant polypeptide having at least 60% sequence identity with any one of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10.
- 15 2. The isolated or recombinant histone deacetylase polypeptide of Claim 1, said polypeptide selected from:
- a) a polypeptide consisting of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10.
- 20 3. The isolated or recombinant histone deacetylase polypeptide of Claim 1, wherein said polypeptide is human.
4. An isolated nucleic acid molecule selected from the group:
- 25 a) an isolated nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9;
- b) a complement of an isolated nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9
- c) an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or
- 30 SEQ ID NO: 10;

- d) a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10;
- 5 e) a nucleic acid that is hybridizeable under high stringency conditions to a nucleic acid molecule that encodes any of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, or SEQ ID NO: 8, or a complement thereof; or
- 10 f) a nucleic acid molecule that is hybridizeable under high stringency conditions to a nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, or SEQ ID NO: 7; and
- g) an isolated nucleic acid molecule that has at least 55% sequence identity with any one of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, or a complement thereof.
- 15 5. The isolated nucleic acid molecule of Claim 4, said nucleic acid molecule consisting of the nucleic acid molecule selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, and SEQ ID NO: 9.
- 20 6. The isolated nucleic acid molecule of Claim 4, wherein said nucleic acid molecule is human.
7. A vector comprising the isolated nucleic acid molecule of Claim 4.
- 25 8. A cell comprising the vector of Claim 7.
9. A cell comprising the isolated nucleic acid molecule of Claim 4.
10. A purified antibody that selectively binds a polypeptide of Claim 1.
- 30 11. A method of identifying a compound that modulates expression of a nucleic acid molecule of Claim 4, said method comprising the steps of:

- a) contacting said nucleic acid molecule with a candidate compound under conditions suitable for expression; and
- b) assessing the level of expression of said nucleic acid molecule, wherein a candidate compound that increases or decreases expression of said nucleic acid molecule relative to a control is a compound that modulates expression of said nucleic acid molecule.
- 5
12. The method of Claim 11, wherein said method is carried out in a cell or animal.
- 10
13. The method of Claim 11, wherein said method is carried out in a cell free system.
14. A method of identifying a compound that modulates the enzymatic activity of the polypeptide of Claim 1, said method comprising the steps of:
- 15
- a) contacting said polypeptide with a candidate compound under conditions suitable for enzymatic reaction; and
- b) assessing the enzymatic activity level of said polypeptide, wherein a candidate compound that increases or decreases the enzymatic activity level of said polypeptide relative to a control is a compound that modulates the enzymatic activity of said polypeptide.
- 20
15. The method of Claim 14, wherein said method is carried out in a cell or animal.
- 25
16. The method of Claim 14, wherein said method is carried out in a cell free system.
17. The method of Claim 14, wherein said polypeptide is further contacted with a substrate for the polypeptide, and wherein said substrate is selected from the group consisting of a cell proliferation disease binding agent, an
- 30

apoptotic disease binding agent, and a cell differentiation disease binding agent.

18. The method of Claim 17, wherein said candidate compound is an inhibitor.
- 5 19. The method of Claim 17, wherein said candidate compound is an activator.
20. A method of identifying a compound that modulates the transcriptional repression activity of the polypeptide of Claim 1, said method comprising
- 10 the steps of:
- a) contacting said polypeptide with a candidate compound under conditions suitable for a transcriptional repression reaction; and
 - b) assessing the transcriptional repression activity level of said polypeptide,
- 15 wherein a candidate compound that increases or decreases the transcriptional repression activity level of said polypeptide relative to a control is a compound that modulates the transcriptional repression activity of said polypeptide.
- 20 21. The method of Claim 20, wherein said method is carried out in a cell or animal.
22. The method of Claim 20, wherein said method is carried out in a cell free system.
- 25 23. The method of Claim 20, wherein said polypeptide is further contacted with a substrate for the polypeptide, and wherein said substrate is selected from the group consisting of a cell proliferation disease binding agent, an apoptotic disease binding agent, and a cell differentiation disease binding agent.
- 30 24. The method of Claim 23, wherein said candidate compound is an inhibitor.

25. The method of Claim 23, wherein said candidate compound is an activator.
26. A method of identifying a compound that modulates expression of a nucleic acid molecule of Claim 4, said method comprising the steps of:
- 5 a) providing a nucleic acid molecule comprising a promoter region of said nucleic acid of Claim 4 or part of a promoter region of said nucleic acid of Claim 4 operably linked to a reporter gene;
- b) contacting said nucleic acid molecule or with a candidate compound; and
- 10 c) assessing the level of said reporter gene,
- wherein a candidate compound that increases or decreases expression of said reporter gene relative to a control is a compound that modulates expression of said nucleic acid molecule of Claim 4.
- 15 27. The method of Claim 26, wherein said method is carried out in a cell.
28. A method of identifying a polypeptide that interacts with a polypeptide of Claim 1 in a yeast two-hybrid system, said method comprising the steps of:
- a) providing a first nucleic acid vector comprising a nucleic acid molecule encoding a DNA binding domain and said polypeptide of Claim 1;
- 20 b) providing a second nucleic acid vector comprising a nucleic acid encoding a transcription activation domain and a nucleic acid encoding a test polypeptide;
- 25 c) contacting said first nucleic acid vector with said second nucleic acid vector in a yeast two-hybrid system; and
- d) assessing transcriptional activation in said yeast two-hybrid system, wherein an increase in transcriptional activation relative to a control indicates that the test polypeptide is a polypeptide that interacts with said
- 30 polypeptide of Claim 1.
29. A pharmaceutical composition comprising a polypeptide of Claim 1.

30. A method of diagnosing a cell proliferation disease, an apoptotic disease, or a cell differentiation disease in a subject, said method comprising the steps of:
- 5 a) obtaining a sample from said subject; and
- b) assessing the level of activity or expression of said polypeptide of Claim 1 in said sample, or detecting the level of said nucleic acid molecule of Claim 4,
- 10 wherein if said level is increased relative to a control, then said subject has an increased likelihood of having a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, and wherein if said level is decreased relative to a control, then said subject has a decreased likelihood of having a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.
- 15 31. The method of Claim 30, wherein said level of activity or expression of said polypeptide of Claim 1 in said sample is measured using immunohistochemical techniques.
- 20 32. The method of Claim 30, wherein said level of said nucleic acid molecule of Claim 4 in said sample is measured using *in situ* hybridization techniques.
- 25 33. A method of treating a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, said method comprising administering a compound identified by the method of Claim 14.
- 30 34. A method of treating a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, said method comprising administering a compound identified by the method of Claim 20.

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FIG. 1A
FIG. 1B
FIG. 1C
FIG. 1D
FIG. 1E
FIG. 1F
FIG. 1G
FIG. 1H
FIG. 1I
FIG. 1J
FIG. 1K
FIG. 1L
FIG. 1M
FIG. 1N
FIG. 1O

FIG. 1

HDAC93186 bp Coding 151-3186

Exon 1

1 ggggaagaga ggcacagaca cagataggag aagggcaccg gctggagcca cttgcaggac tgagggtttt tgcaacaaaa ccctagcagc ctgaagaact
101 ctaagccaga tgggtgggt ggcagagagc agctcttggc tcagcaaga atgcacagta tgatcagctc agtggatgtg aagtcagaag ttctctgtggg
201 cctggagccc atctcactt tagaccttaag gacagacctc agcatgata tgcctgtgtt ggacctgtt gtccgtgaga agcaattgca gcaggaattt
301 cttcttatcc agcagcagca acaatccag aagcagcttc tgatagcaga gtttcagaaa cagcatgaga acttgacag gcagcaccag gctcagcttc
401 aggagcatat caaggaactt ctaggcataa aacagcaaca agaaactcta gaaaggagc agaaactgga gcagcagagg caagaacagg aagtagagag
501 gcatcgagga gaacagcagc ttctctctct cagaggcaaa gatagaggac gagaagggc agtggcaagt acagaagtta agcagaagct tcaagagttc
601 ctactgacta aatcagcaac gaaagacact ccaactaatg gaaaaaatca ttccgtgagc ggcctatcca agctctgcta caggctgcc caccacacat
701 cattggatca aagctctcca ccccttagtg gaacatctcc atcctacaag tacacattac caggagcaca agatgcaaa gatgatttcc cccctcgaaa
801 aactgcctct gagcccaact tgaaggtgag gtccagggtt aacagaaag tggcagagag gagaagcagc cccttactca ggccgaagga tggaaatggt
7

FIG. 1A

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8
901 GTCACTTCAT TCAAGAAGCG AATGTTTGAG GTGACAGAAT CCTCAGTCAG TAGCAGTTCT CCAGGCTCTG GTCCCACTTC ACCAAACAAT GGGCCAACTG
9
1001 GAAGTGTAC TGAATAATGAG ACTTCGGTTT TGGCCCCCTAC CCCTCATGCC GAGCAAAATGG TTTCACAGCA AGCAATCTA ATTCAATGAAG ATTCCATGAA
9
1101 CCTGCTAAGT CTTTATACTT CTCCTTCTTT GCCCAACATT ACCTTGGGGC TTCCCGCAGT GCCATCCAG CTCAATGCTT CGAATTCAT CAAGAAGAAG
10
1201 CAGAAGTGTG AGAGCGAGAC GCTTAGGCAA GGTGTTCCIC TGCTGGGCA GTATGGAGC AGCATCCGG CATCTCCAG CCACCCTCAT GTTACTTTAG
10
1301 AGGAAAGCC ACCCAACAGC AGCCACCAGG CTCTCCTGCA GCATTATTAA TTGAAGAAC AAATGCGACA GCAAAAGCTT CTTGTAGCTG GTGGAGTTCC
3/173
1401 CTTACATCCT CAGTCTCCCT TGGCAACAAA AGAGAGATT TCACCTGGCA TTAGAGGTAC CCACAAATG CCCCCTACA GACCCCTGAA CCGAACCAGG
11
1501 TCTGCACCTT TGCTCAGAG CAGTTGGCT CAGCTGGTCA TTCAACAGCA ACACCAGCA TTCTTGAGA AGCAGAAGCA ATACCAGAG CAGATCCACA
11
1601 TGAACAACT GCTTTCGAA TCTATTGAAC AACTGAAGCA ACCAGGCAGT CACCTTGAGG AAGCAGAGCA AGAGCTTAC GGGGACCAGG CGATGCAGGA
12
1701 AGACAGAGCG CCCTCTAGT GCAACAGCAC TAGGAGCGAC ACCAGTGCTT GTGTGGAGA CACACTGGGA CAAGTTGGG CTGTGAAGT CAAGGAGGAA
12
1801 CCAGTGGACA GTGATGAAGA TGCTCAGATC CAGGAAATGG AATCTGGGA GCAGGCTGCT TTATGCAAC AGCCTTTCCT GGAACCCAGG CACACACGTG

FIG. 1B

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1901 CGCTCTCTGT GCGCCAAGCT CCGCTGGCTG CGGTTGGCAT GGATGGATTA GAGAAACACC GTCTCGTCTC CAGGACTCAC TCCTCCCTGT CTGCCTCTGT
2001 TTACCTCAC CCAGCAATGG ACCGCCCCCT CCAGCCTGGC TCIGCAACTG CAATTGCCCTA TGACCCCTTG ATGCTGAAAC ACCAGTCCGT TTGTGGCAAT
2101 TCCACCACC ACCCTGAGCA TGCTGGAGCA ATACAGAGTA TCTGGTCAG ACTGCAAGAA CTGGGGCTGC TAAATAAATG TGAGGGAATT CAAGTGGAA
2201 AAGCCAGCCT GGAGGAATA CAGCTTGTTT CACTCACTG TTGTATGGCA CCAACCCCT GGACGGACAG AAGCTGGACC CCAGGATACT
2301 CTAGGTGAT GACTCTCAA AGTTTTTTC CTCAATTACCT TCTGGTGGAC TTGGGGTGGG CAGTGACACC ATTGGAATG AGTACACTC GTCCGGTGCT
2401 GCACGATGG CTGTTGGCTG TGTCAATGAG CTGGCTTCCA AAGTGGCTC AGGAGAGCTG AAGAAATGGT TTGCTGTGT GAGCCCCCT GGCCATCAG
2501 CTGAGAATC CACAGCCATG GGGTCTGTCT TTTTAAATC AGTTGCAAT ACCGCCAAT ACTTGAGACA CCACTAAAT ATAAGCAAGA TATTGATTGT
2601 AGATCTGGAT GTTCAACATG GAAAGGTAC CCAGCAGGCC TTTTATGCTG ACCCCAGCAT CCTGTACAT TCACCTCATC GCTATGATG AGGAACTTT
2701 TTCCCTGGCA GTGGAGCCC AATGAGGTT GGAACAGGCC TTGGAGAAG GTACAATATA AATATTGCCT GGACAGGTGG CCTGATCCT CCCATGGGAG
2801 ATGTTAGTA CCTTGAAGCA TTCAGGacca TCGTGAAGCC TGTGGCCAAA GAGTTTGATC CAGACATGGT CTTAGTATCT GCTGATTG ATGCATTGGA
2901 AGGCCACACC CTCTCTCTAG GAGGTACAA AGTGACGGCA AATGTTTTG GTCATTTGAC GAAGCAATG ATACATTGG CTGATGGAG TGTGGTGTG
3001 GCTCTAGAAG GAGGACATGA TCTCAGACC ATCTGTGATG CATCAGAGC CTGTGTAAAT GCCCTTCTAG GAAATGAGCT GGAGCCACTT GCAGAAGATA
3101 TTCTCCACCA AAGCCGAAT ATGAATGCTG TTATTTCTTT ACAGAAGATC ATTGAATTC AAAGTATGTC TTTAAAGTTC TCTTAA

FIG. 1C

HDAC9a 3499 bp (Coding 151-2790)
Exon

1 ggggaagaga ggcacagaca cagataggag aagggcaccg gctggagcca cttgcaggac tgagggtttt tgcaacaaaa ccctagcagc ctgaagaact

101 ctaagccaga tgggggtggt ggacgagagc agctcttggc tcagcaaaga ATGCACAGTA TGATCAGCTC AGTGGATGTG AAGTCAGAAG TTCTCTGTGGG

201 CCTGGAGCCC ATCTCACCTT TAGACCTAAG GACAGACCTC AGGATGATGA TGCCCGTGGT GGACCCCTGTT GTCCCTGAGA AGCAATTGCA GCAGGAATTA

301 CTTCCTTATCC AGCAGCAGCA ACAAATCCAG AAGCAGCTTC TGATAGCAGA GTTTCAGAAA CAGCATGAGA ACTTGACAGG GCAGCACCAG GCTCAGCTTC

401 AGGAGCATAT CACGGAACCT CTAGCCATAA AACAGCAACA AGAATCCTTA GAAAGGAGC AGAACTGGA GCAGCAGAGG CAAGAACAGG AAGTAGACAG

501 GCATCCGAGA GAACAGCAGC TTCTCTCTCT CAGAGGCAAA GATAGAGGAC GAGAAAGGC AGTGGCAAGT ACAGAAGTAA AGCAGAAGCT TCAAGAGTTC

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FIG. 1D

5
601 CTACTGAGTA AATCAGCAAC GAAAGACACT CCAACTAATG GAAAAATCA TTCCGTGAGC CGCCATCCCA AGTCTGGTA CACGGCTGCC CACCACACAT
6
701 CATTGGATCA AAGCTCTCCA CCCCTTAGTG GAACATCTCC ATCTACAAG TACACATTAC CAGGAGCACA AGATGCAAAG GATGATTTC CCCTTCGAAA
7
801 AACTGCTCT GAGCCCAACT TGAAGGTGG GTCCAGTTA AACAGAAAG TGGCAGAGAG GAGAAGCAGC CCCTTACTCA GCGGAAGGA TGGAAATGTT
9
901 GTCACTTCAT TCAAGAAGC AATGTTTGAG GTGACAGAAAT CCTCAGTCAG TAGCAGTTCT CCAGGCTCTG GTCCCAGTTC ACCAAACAAT GGGCCAACTG
10
1001 GAAGTGTAC TGAANAATGAG ACTTCGGTTT TGCCCCCTAC CCCTCATGCC GAGCAAAATG TTTCACAGCA AGCATTCTA ATTCATGAAG ATTCCAAGAA
11
1101 CCTGCTAAGT CTTTATACCT CTCCTTCTTT GCCCAACATT ACCTTGGGC TTCCGCGAGT GCCATCCCAG CTCATGCTT CGAATTCACT CAAAGAAAAG
12
1201 CAGAAGTGTG AGAGGCAGAC GCTTAGGCAA GGTGTTCTC TGCCTGGCA GTATGGAGGC AGCATCCCG CATCTTCCAG CCACCTCAT GTTACTTTAG
13
1301 AGGGAAGCC ACCCAACAGC AGCCACCAG CTCCTCTGCA GCATTATTA TTGAAGAAC AAATGGACA GCAAAGCTT CTTGTAGCTG GTGGAGTTCC
14
1401 CTTACATCCT CAGTCTCCCT TGGCAACAAA AGAGAGAATT TCACCTGGCA TTAGAGGTAC CCACAAATG CCCCCTCACA GACCCCTGAA CCGAACCCAG
15
1501 TCTGCACCTT TGCCTCAGAG CAGGTTGGCT CAGCTGGTCA TTCAACAGCA ACACCAGCA TTCTTGGACA AGCAGAACCA ATACCAGAG CAGATCCACA

FIG. 1E

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1601 TGAACAACT GCTTTCGAAA TCTATTGAAC AACTGAAGCA ACCAGGCAGT CACCTTGAGG AAGCAGAGGA AGACTTTCAG GGGGACCAGG CGATGCAGGA
1701 AGACAGAGCG CCCCTCTAGTG GCAACAGCAC TAGGAGCGAC AGCAGTGCCT GTGTGGATGA CACACTGGGA CAAGTTGGGG CTGTGAAGGT CAAGGAGGAA
1801 CCAGTGGACA GTGATGAAGA TGCTCAGATC CAGGAAATGG AATCTGGGGA GCAGGCTGCT TTTATGCAAC AGCCTTTCCT GGAACCCACG CACACACGTG
1901 CGCTCTCTGT GCGCCAGAGT CCGCTGGCTG CGGTTGGCAT GGATGGATTA GAGAAACACC GTCTCGTCTC CAGGACTCAC TCTTCCCCCTG CTGCCCTCTGT
2001 TTTACCTCAC CCAGCAATGG ACCGCCCCCT CCAGCCTGGC TCTGCAACTG GAATTCCTTA TGACCCCTTG ATGCTGAAAC ACCAGTGCCT TTGTGGCAAT
2101 TCCACCACCC ACCCTGAGCA TGCTGGACCA ATACAGAGTA TCTGGTCAAG ACTGCAAGAA ACTGGGCTGC TAATAAATG TGAGCGAATT CAAGGTGGA
2201 AAGCCAGCCT GGAGGAATA CAGCTTGTTT CACTCAGCA TCACCTCACTG TTGTATGGCA CCAACCCCTT GGACGGACAG AAGCTGGACC CCAGGATACCT
2301 CCTAGTGAT GACTCTCAA AGTTTTTTTCTCATTACCT TGTGGTGGAC TTGGGGTGGC CAGTGACACC ATTTGGAATG AGTACACTC GTCCGCTGCT
2401 GCACCATGG CTGTGGCTG TGTATGAG CTGGCTTCCA AAGTGGCTC AGGAGAGCTG AAGATGGGT TTGCTGTGTG GAGGCCCTT GGCCATCAG
2501 CTGAGAATC CACGCCATG GGGTCTGCT TTTTAAATC ACTTGCAATT ACCGCCAAT ACTTGAGAGA CCACTAAAT ATAAGCAAGA TATTGATGT

FIG. 1F

21
2601 AGATCTGGAT GTTCACCATG GAAACGGTAC CCAGCAGGCC TTATTGCTG ACCCCAGCAT CTTGTACATT TCATCCATC GCTATGATGA AGGGAACCTTT

2701 TTCCCTGGCA GTGAGGCC AAATGAGTT CCGTTTATT CTTTAGAGCC CCACCTTTAT TTGTATCTTT CAGGTAATTG CATTGCATGA ttacccttaa
STOP CODON

22
2801 tttttctgtc ctttgctggt gttttaatt acacgagatt actgaattgt cccatgggac caagaaccag tgcagaacaa gtgcataacc cagagcactg

2901 tttgtcaggg aagggtgggc tgatttgatg tgtttatttc aagagctccc atgtgcttgt tttcctctct tcttgcttcc ttccatttgc

23
3001 tctcttctct gccacaccgt gtgtgtcttt ctcttcccag gttggaacag gccttgaga aggtataaat ataaatattg cctggacagg tggccttgat

3101 cctcccatgg gagatgttga gtacctgaa gcattcagga ccactgtgaa gcctgtggcc aaagagtgtg atccagacat ggtcttagta tctgtggat

24
3201 ttgatgcatt ggaagggcac accctctctc taggagggtg caaagtgcg gcaaaatggt ttggtcattt gacgaagcaa ttgatgacat tggtgatgg

25
3301 acgtgtggtg ttggctctag aaggaggaca tgatctcaca gccatctgtg atgcatacga agcctgtgta atgccccttc taggaatga gctggagcca

26
3401 cttgcagaag atattctcca ccaaagcccg aatatgaatg cbgttatttc ttacagaag atcattgaaa ttcaagat gtctttaag ttctcttaa

FIG. 1G

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>HDRP (deltaNLS)

1	ggggaagaga	ggcacagaca	cagataggag	aaggccaccg	gctggagcca
51	cttgcaggac	tgagggtttt	tgcaacaaaa	ccctagcagc	ctgaagaaat
101	ctaagccaga	tggggtggct	ggacgagagc	agctcttggc	tcagcaaaaga
151	atgcacagta	tgatcagctc	agtgatgtg	aagtcagaag	ttcctgtggg
201	cctggagccc	atctcacctt	tagacctaa	gacagacctc	aggatgatga
251	tgcccggtgt	ggaccctgtt	gtccgtgaga	agcaattgca	gcaggaattta
301	cttcttatcc	agcagcagca	acaaatccag	aagcagcttc	tgatagcaga
351	gttcagaaa	cagcatgaga	acttgacacg	gcagcaccag	gctcagcttc
401	aggagcatat	caagggaactt	ctagccataa	aacagcaaca	agaactccta
451	gaaaaggagc	agaaactgga	gcagcagagg	caagaacagg	aagtagagag
501	gcctcgcaga	gaacagcagc	ttctctctct	cagaggcaaa	gatagaggac
551	gagaaagggc	agtggcaagt	acagaagtaa	agcagaagct	tcaagagttc
601	ctactgagta	aatcagcaac	gaaagacact	ccaaactaatg	gaaaaaatca
651	ttccgtgagc	cgccatccca	agctctggta	cacggctgcc	caccacacat
701	catgggatca	aagctctcca	ccccttagtg	gaacatctcc	atcctacaag
751	tacacattac	caggagcaca	agatgcaaa	gatgatttcc	cccttcgaaa
801	aactgaatcc	tcagtcagta	gcagttctcc	aggctctggt	ccagttcac
851	caaacaatgg	gccaaactgga	agtgttactg	aaatgagac	ttcgggtttg
901	ccccctaccc	ctcatgccga	gcaaattggtt	tcacagcaac	gcatttcta
951	tcatgaagat	tccatgaacc	tgctaagtct	ttatacctct	ccctctttgc
1001	ccaacattac	cttgggggctt	cccgcagtgc	catcccagct	caatgcttcg

FIG. 1H

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1051 aattcactca aagaaaagca gaagtgtgag acgcagacgc ttaggcaagg
1101 tgttcctctg cctgggcagt atggaggcag catcccgga tcttccagcc
1151 accctcatgt tactttagag ggaagccac ccaacagcag ccaccaggct
1201 ctccctgcagc atttattatt gaaagaacaa atgcgacagc aaaagcttct
1251 tgtagctggt ggagttccct tacatcctca gtctcccttg gcaacaaaag
1301 agagaatttc acctggcatt agaggtaccc acaaattgcc ccgtcacaga
1351 cccctgaacc gaaccagtc tgcacctttg cctcagagca cgttggtca
1401 gctggtcatt caacagcaac accagcaatt cttggagaag cagaagcaat
1451 accagcagca gatccacatg acaaaactgc ttcgaaatc tattgaacaa
1501 ctgaagcaac caggcagtca cttgaggaa gcagagggaag agcttcaggg
1551 ggaccaggcg atgcaggaa acagagcgcc ctctagtggc aacagcacta
1601 ggagcgacag cagtgttgt gtggatgaca cactgggaca agttggggct
1651 gtgaagggtca aggaggaacc agtggacagt gatgaagatg ctcatatcca
1701 ggaaatggaa tctggggagc aggctgcttt tatgcaacag gtaataggca
1751 aagatttagc tccaggattt gtaattaaag tcattatctg a

FIG. 11

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>HDAC9 (deltaNLS)

```

1  ggggaagaga  ggcacagaca  cagataggag  aaggcacccg  gctggagcca
51  ctgcaggac   tgagggtttt  tgcaacaaaa  ccttagcagc  ctgaagaact
101 ctaagccaga  tggggtggct  ggacgagagc  agctcttggc  tcagcaaaaga
151 atgcacagta  tgatcagctc  agtggatgtg  aagtcagaag  ttcctgtggg
201 cctggagccc  atctcacctt  tagacctaa  gacagacctc  aggatgatga
251 tgcccgtggt  ggaccctgtt  gtccgtgaga  agcaattgca  gcaggaatta
301 cttcttatcc  agcagcagca  acaaatccag  aagcagcttc  tgatagcaga
351 gtttcagaaa  cagcatgaga  acttgacacg  gcagcacccg  gctcagcttc
401 aggagcatat  caaggaactt  ctagccataa  aacagcaaca  agaactccta
451 gaaaaggagc  agaaactgga  gcagcagagg  caagaacagg  aagtagagag
501 gcatcgcaga  gaacagcagc  ttctctctct  cagaggcaaa  gatagaggac
551 gagaaagggc  agtggcaagt  acagaagtaa  agcagaagct  tcaagagttc
601 ctactgagta  aatcagcaac  gaaagacact  ccaactaatg  gaaaaaatca
651 ttccgtgagc  cgccatccca  agctctggta  cacggctgcc  caccacacat
701 cattggatca  aagctctcca  ccccttagtg  gaacatctcc  atcctacaag
751 tacacattac  caggagcaca  agatgcaaa  gatgatattcc  cccttcgaaa
801 aactgaatcc  tcagtcagta  gcagttctcc  aggctctggt  ccagttcac
851 caaacaaatgg  gccaaactgga  agtgttactg  aaatgagac  ttcggttttg
901 cccctaccc  ctcatgccga  gcaaatgggt  tcacagcaac  gcattctaat
951 tcatgaagat  tccatgaacc  tgctaagtct  ttataacctt  ccttctttgc
1001 ccaacattac  cttggggctt  cccgcagtgc  catcccagct  caatgcttcg
1051 aattcactca  aagaaaaagca  gaagtgtgag  acgcagacgc  ttaggcaagg
1101 tgttcctctg  cctgggcagt  atggaggcag  catccgggca  tttccagcc

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FIG. 1J

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1151 accctcatgt tactttagag ggaaagccac ccaacagcag ccaccaggct-
1201 ctccctgcagc atttattattt gaaagaacaa atgcgacagc aaaagcttct
1251 tgtagctggt ggagttccct tacatcctca gtctcccttg gcaacaaaag
1301 agagaatttc acctggcatt agaggtacct aaaaattgcc ccgtcacaga
1351 ccctgaacc gaaccagtc tgcaccttg cctcagagca cgttgggtca
1401 gctgggtcatt caacagcaac accagcaatt cttggagaag cagaagcaat
1451 accagcagca gatccacatg aaaaaactgc ttccgaaatc tattgaacaa
1501 ctgaagcaac caggcagtc cttgaggaa gcagagggaag agcttcaggg
1551 ggaccaggcg atgcaggaag acagagcgcc ctctagtggc aacagcacta
1601 ggagcgacag cagtgttgt gtggatgaca cactgggaca agttggggct
1651 gtgaagggtca aggaggaacc agtggacagt gatgaagatg ctcagatcca
1701 ggaaatggaa tctggggagc aggtgtgtt tatgcaacag cctttccttg
1751 aaccacgcga cacagtgcg ctctctgtgc gccaaagctcc gctgggtgcg
1801 gttggcatgg atggattaga gaaacaccgt ctctgtcca ggactcactc
1851 ttcccctgct gcctctgtt tacctcacc agcaatggac cgccccctcc
1901 agcctggctc tgcaactgga attgcctatg accccttgat gctgaaacac
1951 cagtgcgttt gtggcaattc caccacccac cctgagcatg ctggacgaat
2001 acagagtatc tggtcacgac tgcaagaaac tgggctgcta aataaatgtg
2051 agcgaattca aggtcgaaaa gccagcctgg aggaatatca gcttgttcat
2101 tctgaacatc actcactgtt gtatggcacc aaccccctgg acggacagaa
2151 gctggacccc aggatactcc taggtgatga ctctcaaaag tttttttcct
2201 cattaccttg tggtgactt ggggtggaca gtgacaccat ttggaatgag
2251 ctacactcgt ccggtgctgc acgcatggct gttggctgtg tcatcgagct
2301 ggcttccaaa gtggcctcag gagagctgaa gaatgggttt gctgttgtga
2351 ggccccctgg ccatcacgt gaagaatcca cagccatggg gttctgcttt
2401 ttttaattcag ttgcaattac cgccaaatac ttgagagacc aactaaatat

FIG. 1K

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```
2451 aagcaagata ttgattgtag atctggatgt tcaccatgga aacgggtaccc  
2501 agcaggcctt ttatgctgac ccagcatedc tgtacatttc actccatcgc  
2551 tatgatgaag ggaacttttt ccctggcagt ggaagcccaa atgagggttgg  
2601 aacaggcctt ggagaagggg acaataaaa tattgcctgg acagggtggcc  
2651 ttgatcctcc catgggagat gttgagtacc ttgaagcatt caggaccatc  
2701 gtgaagcctg tggccaaaga gtttgatcca gacatggctc tagtatctgc  
2751 tggatttgat gcattggaag gccacacccc tcctctagga gggtaaaaag  
2801 tgacggcaaa atgttttggg catttgacga agcaattgat gacattggct  
2851 gatggacgtg tgggtgttggc tctagaagga ggacatgata tcacagccat  
2901 ctgtgatgca tcagaagcct gtgtaaatgc cttctagga aatgagctgg  
2951 agccacttgc agaagatat ctccaccaa gcccgaaat gaatgctgtt  
3001 atttctttac agaagatcat tgaaattcaa agtatgtctt taaagttctc  
3051 ttaa
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FIG. 1L

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>HDAC9a (deltaNLS)

1	ggggaagaga	ggcacagaca	cagataggag	aagggcaccg	gctggagcca
51	cttgaggag	tgagggtttt	tgcaacaaaa	ccctagcagc	ctgaagaact
101	ctaagccaga	tggggtggct	ggacgagagc	agctcttggc	tcagcaaaaga
151	atgcacagta	tgatcagctc	agtggatgtg	aagtcagaag	ttcctgtggg
201	cctggagccc	atctcacctt	tagacctaa	gacagacctc	aggatgatga
251	tgcccgtggt	ggaccctgtt	gtccgtgaga	agcaattgca	gcaggaaatta
301	cttcttatcc	agcagcagca	acaaatccag	aagcagcttc	tgatagcaga
351	gtttcagaaa	cagcatgaga	acttgacacg	gcagcaccag	gctcagcttc
401	aggagcatat	caaggaaactt	ctagccataa	aacagcaaca	agaactccta
451	gaaaaggagc	agaaactgga	gcagcagagg	caagaacagg	aagtagagag
501	gcatacgaga	gaacagcagc	ttctctctct	cagaggcaaa	gatagaggac
551	gagaaagggc	agtggcaagt	acagaagtaa	agcagaagct	tcaagagttc
601	ctactgagta	aatcagcaac	gaaagacact	ccaactaatg	gaaaaaatca
651	ttccgtgagc	cgccatccca	agctctggtg	cacggctgcc	caccacacat
701	cattggatca	aagctctcca	ccccttagtg	gaacatctcc	atcctacaag
751	tacacattac	caggagcaca	agatgcaaa	gatgatttcc	cccttcgaaa
801	aactgaatcc	tcagtcagta	gcagttctcc	aggctctggt	ccagttcac
851	caaacaatgg	gccaaactgga	agtgttactg	aaaatgagac	ttcgggttttg
901	ccccctaccc	ctcatgccga	gcaaatgggt	tcacagcaac	gcatttctaata
951	tcataaagat	tcatagaacc	tgctaagtct	ttatacctct	ccttctttgc
1001	ccaacattac	cttggggcctt	cccgcagtgc	catcccagct	caatgcttgc
1051	aattcactca	aagaaaagca	gaagtgtgag	acgcagacgc	ttaggcaagg
1101	tgttcctctg	cctggggcagt	atggaggcag	catcccgga	tcttcagcc
1151	accctcatgt	tacttttagag	ggaaagccac	ccaacagcag	ccaccaggct

FIG. 1M

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1201 ctccctgcagc atttattatt gaaagaacaa atgcgacagc aaaagcttct
1251 tctagctgggt ggagttccct tacatcctca gtctcccttg gcaacaaaag
1301 agagaatttc acctggcatt agaggtacct agaggtgcc ccgtcacaga
1351 ccctgaacc gaaccagtc gaaccctttg tgcacctttg cctcagagca cgttggtca
1401 gctggtcatt caacagcaac accagcaatt ctgggagaag cagaagcaat
1451 accagcagca gatccacatg acaaaactgc ttctgaaatc tattgaacaa
1501 ctgaagcaac caggcagtca ccttgaggaa gcagaggaag agcttcaggg
1551 ggaccaggcg atgcaggaag acagagcgcc ctctagtggc aacagcacta
1601 ggagcgacag cagtgttgt gtggatgaca cactgggaca agttggggct
1651 gtgaagggtca aggaggaacc agtggacagt gatgaagatg ctcagatcca
1701 gaaaatggaa tctggggagc aggtgcttt tatgcaacag cctttcctgg
1751 aaccacgca cacacgtcg cctctgtgc gccaaactcc gctggctgcg
1801 gttggcatgg atggattaga gaaacacgt ctgctcca ggactcactc
1851 tccccctgct gcctctgttt tacctcacc agcaatggac cgccccctcc
1901 agcctggctc tgcaactgga attgcctatg acccctgat gctgaaacac
1951 cagtgcgttt gtggcaattc caccacccac cctgagcatg ctggacgaat
2001 acagagtatc tggtcacgac tgcaagaaac tgggctgcta aataaatgtg
2051 agcgaattca aggtcgaaaa gccagcctgg aggaaataca gcttgttcat
2101 tctgaacatc actcactgtt gtatggcacc aacccctgg acggacagaa
2151 gctggacccc aggatactcc taggtgatga ctctcaaaag tttttttcct
2201 cattaccttg tggaggactt ggggtggaca gtgacaccat ttggaatgag
2251 ctacactcgt ccggtgctgc acgcatggct gttggctgtg tcatcgagct
2301 ggcttccaaa gtggcctcag gagagctgaa gaatgggttt gctgttgtga
2351 ggccccctgg ccatacagct gaagaatcca cagccatggg gttctgcttt
2401 ttttaattcag ttgcaattac cgccaaatac ttgagagacc aactaaatat

FIG. 1N

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2451 aagcaagata ttgattgtag atctggatgt tcaccatgga aacggtaccc
2501 agcaggccctt ttatgctgac ccagcatcc tgtacatttc actccatcgc
2551 tatgatgaag ggaacttttt cctggcagt ggagcccaa atgaggttcg
2601 gtttatttct ttagagcccc acttttattt gtatctttca ggtaattgca
2651 ttgcatgatt accctaatt ttcttgctct ttgctggtgt tttaaattac
2701 acgagattac tgaattgtcc catgggacca agaaccagtg cagaacaagt
2751 gcataaacca gagcactgtt tgtcaggaa ggttgggctg atttgatgtg
2801 ttgtttgatg tttatttcaa gagctcccat gtgcttgttt tcctctcttc
2851 ttgcttttct ccatctgctc tcttctctgc ccaccgtggt gtgtctttct
2901 cttcccaggt tggaaacagg cttggagaag ggtacaatat aaatatgccc
2951 tggacagggt gccttgatcc tcccatggga gatgtgagt accttgaagc
3001 attcaggacc atcgtgaagc ctgtggccaa agagtttgat ccagacatgg
3051 tcttagtata tgctggattt gatgcattgg aaggccacac ccctcctcta
3101 ggaggggtaca aagtgcggc aaaatgtttt ggtcatttga cgaagcaatt
3151 gatgacattg gctgatggac gtgtggtgtt ggctctagaa ggaggacatg
3201 atctcacagc catctgtgat gcatcagaag cctgtgtaaa tgcccttcta
3251 ggaaatgagc tggagccact tgcagaagat attctccacc aaagcccga
3301 tatgaatgct gttatttctt tacagaagat cattgaaatt caaagtatgt
3351 ctttaaaagt ctcttaa
```

FIG. 10

FIG. 2A
FIG. 2B
FIG. 2C
FIG. 2D
FIG. 2E

FIG. 2

>HDAC9 (1011 amino acids)
MHSMISSVDVKSEVPVGLPI SPLDLRTDLRMMMPVDPVREKQLQQLLLIQQQQOI
QKQLLIAEFQKHENLTRHQQAQLQEHIKELLAIKQQQELLEKEQKLEQQRQEQEVERH
RREQQLPPLRGKDRGRERAVASTEYKQKLQEFLLSKSATKDTPTNGKNHVSRRHPKLWY
TAAHHTSLDQSSPPLSGTSPSYKTYTLPGAQDAKDDFPLRKTASEPNLKVRSRLKQKVAE
RRSPLLRRKDGNVVTSFKKRMFEVTESVSSSSPGSGSPNNNGPTGSVTENETSVLP
PTPHAEQMVVSQQRILIHEDSMNLLSLYTSPSLPNITGLPAVPSQLNASNSLKEKQKCE
TQTLRQGVPLPGQYGGSI PASSSHPHVTLEGKPPNSSHQALLQHLLLKEQMRQQKLLVA
GGVPLHPQSPLATKERISPGIRGTHKLP RHRPLNRTQSAPLPQSTLAQLVIOQQHQQFL
EKQKQYQQQIHMNKLKLSIEQLKQPGSHLEEAEEEEELQGDQAMQEDRAPSSGNSTRSDS
SACVDDTLGQVGAVKVEEPVDSDEDAQIQEMESGEQA AFMQQPFLEPTHTRALSVRQA
PLA AVGMDGLEKHLVSRTHSSPAASVLPHPAMDRLPQPGSATGIA YDPLMLKHQCVCG
NSTTHPEHAGRIQSIWSRLQETGLLNKCE RIQGRKASLEEIQLVHSEHHSLLYGTNP LD
GQKLDPRILLGDDSQKFFSSLPCGGLGVDSDTIWNELHSSGAARMAVGCVIELASKVAS
GELKNGFAVVRPPCHHAAEEESTAMGFCFFNSVAITAKYLRDQLNISKILIVDLDVHHGNG
TQQAFYADPSILYISLHRYDEGNFFPGSGAPNEVGTGLGEGYNININIAWTGGLDPPMGDV
EYLEAFRTIVKPVAKFDPDMVLVSAGFDAL EGHTPPLGGYKVTA KCFGHLTKQLMTLA
DGRVVLAL EGGHDLTAICDASEACVNALLGNELEPLAEDILHQSPNMNAVISLQKIEI
QSM SLKFS

FIG. 2A

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>HDAC9a (879 amino acids)
MHSMISSVDVKSEVPVGLPEISPLDLRTDLRMMMPVDPVREKQLQQLLELLIQQQQI
QKQLLIAEFQKQHENLTRQHQAQLQEHIKELLAIKQQQELLEKEQKLEQQRQEQEVERH
RREQQLPPLRGKDRGRERAVASTEVKQLQEFLLSKSATKDTPTNGKNHSVSRHPKLVY
TAAHHTSLDQSSPPLSGTSPSYKYTLPGAQDAKDDEFPLRKTASEPNLKVRSRLKQKVAE
RRSSPLLRRKDGNVVTSFKKRMFEVTESSVSSSPGSPSPNNGPTGSVTENETSVLP
PTPHAEQMVVSQQRILIHEDSMNLLSLYTSPSLPNITLGLPAVPSQLNASNSLKEKQKCE
TQTLRQGVPLPGQYGGSI PASSSHPHVTLEGKPPNSSHQALLQHLLLEQMRQKLLVA
GGVPLHPQSPLATKERISPGIRGTHKLPRHRPLNRTQSAPLPQSTLAQLVIOQQHQQFL
EKQKQYQQQIHMNKLKLSKIEQLKQPGSHLEEAEEEEELQGDQAMQEDRAPSSGNSTRSDS
SACVDDTLGQVGAVKKEEPVDSDEDAQIQEMESGEQAAMQPPFLEPTHTTRALSVRQA
PLAAVGMGDLKHLVSRTHSSPAASVLPHPAMDRPLQPGSATGIAYDPLMLKHQCVCG
NSTTHPEHAGRIQSIWSRLQETGLLNKCERIQGRKASLEEIQLVHSEHSLLYGTNPLD
GQKLDPRILLGDDSQKFFSSLPCCGLGVDSDTIWNELHSSGAARMVGCVIELASKVAS
GELKNGFAVVVRPPGHHAEEESTAMGFCFFNSVAITAKYLRDQLNISKILIVDLDVHHGNG
TQQAFYADPSILYISLHRYDEGNFFPGSGAPNEVRFISLEPHFYLYLSGNCIA

FIG. 2B

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>HDAC9 (ANLS) (967 amino acids)
MHSMISSVDVKSEVPVGLPI SPLDLRTDLRMMMPVDPVVRKQLQQLLELLLIQQQQQI
QKQLIAEFQKQHNLTRQHQAQLQEHIKELLAIKQQQELLEKEQKLEQQRQEQEVERH
RREQQLPPLRGKDRGRERAVASTEVKQLQEFLLSKSATKDTPTNGKNHSVSRHPKLWY
TAAHHTSLDQSSPPLSGTSPSYKYTLPGAQDAKDDFPLRKTESSVSSSSPGSGPSSPNN
GPTGSVTENETSVLPPTPHAEQMV SQORILIHEDSMNLLSLYTSPLPNI TLGLPAVPS
QLNASNSLKEKQKCEQTQTLRQGVPLPGQYGGSI PASSSHPHVTLEGKPPNSSHQALLQH
LLLKEQMRQQLLVAGGVPLHPQSPPLATKERISPGIRGTHKLP RHRPLNRTQSA PLPQS
TLAQLVIQQHQHFLEKQKQYQQQIHMNKL LSKSIEQLKQPGSHLEEAEEELQGDQAMQ
EDRAPSSGNSTRSDSSACVDDTLGQVGAVKVKKEPVDSDEDAQIQEMESGEQA AFMQQP
FLEPTHTRALSVRQAPLA AVGMDGLEKHRLVSRTHSSPAASVLPHPAMDRPLQPGSATG
IAYDPLMLKHQCVCGNSTTHPEHAGRIQSIWSRLQETGLLNKCERIQGRKASLEEIQLV
HSEHHSLLYGTNPLDGQKLDPRILLGDDSQKFFSSLPCCGLGVDSDTIWNELHSSGAAR
MAVGCVIELASKVASGELKNGFAVVRPPGHHAEESTAMGFCFFNSVAITAKYLRDQLNI
SKILIVDLDVHHGNGTQQA FYADPSILYISLHRYDEGNFFPGSGAPNEVGTGLGEGYNI
NIAWTGGLDPPMGDVEYLEAFRTIVKPVAKFEFDPDMVLVSAGFDAL EGTPTPLGGYKVT
AKCFGHLTKQLMTLADGRVVLALEGGHDLTAICDASEACVNALLGNELEPLAEDILHQS
PNMNAVISLQKIIIEIQMSLSLKFS

FIG. 2C

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>HDAC9a (ANLs) (835 amino acids)
MHSMISSVDVKSEVPVGLPI SPLDLRTDLRMMMPVDPVREKQLQQLLLIQQQQI
QKQLLIAEFQKQHENLTRHQQAQLQEHIKELLAIKQQQLLEKEQKLEQQRQEQEVERH
RREQQLPPLRGKDRGRERAVASTEYKQKLQEFLLSKSATKDTPTNGKNHVSVRHPKLWY
TAAHHTSLDQSSPPLSGTSPSYKYTLPGAQDAKDDFPLRKTESSVSSSPGSGPSSPNN
GPTGSVTENETSVLPPTPHAEQMVSQQRILIHEDSMNLLSLYTSPLPNI TLGLPAVPS
QLNASNSLKEKQKCETQTLRQGVPLPGQYGGSI PASSSHPHVTTLEGKPPNSSHQALLQH
LLLKEQMRQKLLVAGGVPLHPQSPLATKERISPGIRGTHKLP RHRPLNRTQSA PLPQS
TLAQLVIQQQHQQFLEKQKQYQQQIHMNKL LSKSIEQLKQPGSHLEEAEEELQGDQAMQ
EDRAPSSGNSTRSDSSACVDDTLGQVGAVKVKEEPVDSDEDAIQEMESGEQA AFMQQP
FLEPHTRALSVRQAPLAAVGM DGLEK HRLVSRTHSSPAA SVLPHPAMDRPLQPGSATG
IAYDPLMLKHQCVCGNSTTHPEHAGRIQSIWSRLQETGLLNKCE RIQGRKASLEEIQLV
HSEHHSLLYGTNPLDGQKLDPRILLGDDSQKFFSLLPCGGLGVDSDTIWNELHSSGAAR
MAVGCVIELASKVASGELKNGFAVVRPPGHHAEEESTAMGFCFFNSVAITAKYLRDQLNI
SKILIVDL DVHHGNGTQQAFYADPSILYISLHRYDEGNFFPGSGAPNEVRFISLEPHFY
LYLSGNCIA

FIG. 2D

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>HDRPa (HDRP ΔNLS) (546 amino acids)
MHSMISSVDVKSEVPVGLPEISPLDLRTDLRMMMPVVDPVVREKQLQQELLIIQQQQQI
QKQLLIAEFQKHENLTRQHQAQLQEHIKELLAIKQQQELLEKEQKLEQQRQEQEVERH
RREQQLPPLRGKDRGRERAVASTEVKQLQEFLLSKSATKDTPTNGKNHSVSRHPKLWY
TAAHHTSLDQSSPPLSGTSPSYKYITLPGAQDAKDDFPLRKTESSVSSSPGSGPSSPNN
GPTGSVTENETSVLPPTPHAEQMVSQQRILIHEDSMNLLSLYTSPSLPNI TLGLPAVPS
QLNASNSLKEKQKCETQTLRQGVPLPGQYGGSI PASSSHPHVTLEGKPPNSSHQALLQH
LLLKEQMRQOKLLVAGVPLHPQSPLATKERISPGIRGTHKLP RHRPLNRTQSAPI PQS
TLAQLVIQQQHQQFLEKQKQYQQQIHMNKLKSKSIEQLKQPGSHLEEAEEELQGDQAMQ
EDRAPSSGNSTRSDSSACVDDDTLGQVGAVKVKEEPVDSDEDAQIQEMESGGEQA AFMQQV
IGKDLAPGEVVKVII

FIG. 2E

FIG. 3A
FIG. 3B
FIG. 3C

FIG. 3

FIG. 3A

HDRP	1	-----	MHSMISSVDVKSEVPVGLPEP	-----	ISPLDLRLTDLRMMMP
HDAC9a	1	-----	MHSMISSVDVKSEVPVGLPEP	-----	ISPLDLRLTDLRMMMP
HDAC9	1	-----	MHSMISSVDVKSEVPVGLPEP	-----	ISPLDLRLTDLRMMMP
HDAC4	1	MSSQSHPDGLSGRDQPVVELNPAR	VNHMPSTIVDVATAPLQVAPSAVENDLRDHFSLPE		
HDRP	36	VVDPVVRREKLOOELLII00000I	OKOLLIAEFKOKOHENLTROHQAOLOEHIK	---	ELLA
HDAC9a	36	VVDPVVRREKLOOELLII00000I	OKOLLIAEFKOKOHENLTROHQAOLOEHIK	---	ELLA
HDAC9	36	VVDPVVRREKLOOELLII00000I	OKOLLIAEFKOKOHENLTROHQAOLOEHIK	---	ELLA
HDAC4	61	VAFPAIRREQQLOOELLALIKQKQOIQRQILIAEFQRQHEQLSRQHEAQLFHEHIKQQQ	EMLA		
HDRP	93	IKOOOELLEKEOKLEOOROEVEVRRRREOOLPPLRGKDRGRERAVASTEVEVKOKLOEFFLL			
HDAC9a	93	IKOOOELLEKEOKLEOOROEVEVRRRREOOLPPLRGKDRGRERAVASTEVEVKOKLOEFFLL			
HDAC9	93	IKOOOELLEKEOKLEOOROEVEVRRRREOOLPPLRGKDRGRERAVASTEVEVKOKLOEFFLL			
HDAC4	121	MKHQOELLEHEHQRLERHRQOEELKEKQREHQIQQLLKNNKEKKEKESAVASTEVEVKOKLOEFFVL			
HDRP	153	SKSATKDTPTNGKNHVSVRHPKLWYTAAHHTSLDQSSPPLSGTSPSYKYTLPGAQDAKDD			
HDAC9a	153	SKSATKDTPTNGKNHVSVRHPKLWYTAAHHTSLDQSSPPLSGTSPSYKYTLPGAQDAKDD			
HDAC9	153	SKSATKDTPTNGKNHVSVRHPKLWYTAAHHTSLDQSSPPLSGTSPSYKYTLPGAQDAKDD			
HDAC4	181	NK- -KKALAHRNINHCISSDPRWYCKTQHSISLDQSSPPQSGVSTSYNHPVLGMYDAKDD			
HDRP	213	FPLRKTASEP NLKVR SRLKOKVAERRSSP LLRRKDG NVVT SFKKRMFEVTESVSSSSSPG			
HDAC9a	213	FPLRKTASEP NLKVR SRLKOKVAERRSSP LLRRKDG NVVT SFKKRMFEVTESVSSSSSPG			
HDAC9	213	FPLRKTASEP NLKVR SRLKOKVAERRSSP LLRRKDG NVVT SFKKRMFEVTESVSSSSSPG			
HDAC4	239	FPLRKTASEP NLKVR SRLKOKVAERRSSP LLRRKDG PVVTALIKRPLDVTDSACSS-APG			

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HDRP	273	SGPSSPNNNGPTG	SVTENETSVLPPT	PHAEOMVSOORIL	IHEDSMNLLSL	YTS	SPSLPNITL
HDAC9a	273	SGPSSPNNNGPTG	SVTENETSVLPPT	PHAEOMVSOORIL	IHEDSMNLLSL	YTS	SPSLPNITL
HDAC9	273	SGPSSPNNNGPTG	SVTENETSVLPPT	PHAEOMVSOORIL	IHEDSMNLLSL	YTS	SPSLPNITL
HDAC4	298	SGPSSPNNSSGS	VSAENGIAPAVPS	IPAEITSLAHR	-LVAREGSAAPL	PLYTS	SPSLPNITL
HDRP	333	GLPAVPSOLNAS	SLKEKOKCETOTL	ROGVPLPGOYGG	SI	PASSSSHPHV	TLEGKPPNSSH
HDAC9a	333	GLPAVPSOLNAS	SLKEKOKCETOTL	ROGVPLPGOYGG	SI	PASSSSHPHV	TLEGKPPNSSH
HDAC9	333	GLPAVPSOLNAS	SLKEKOKCETOTL	ROGVPLPGOYGG	SI	PASSSSHPHV	TLEGKPPNSSH
HDAC4	357	GLPATGPSAGT	AGQQ-DIERLTL	PAQQORLSL	FFGTHLIPYL	STIS	-PIERDG--GAAH
HDRP	393	OALLQHLLLL	KEOMROOKLL	VAGG--VPLH	POSPLATKERI	SPGIRG	THKLPRHRPLNRTO
HDAC9a	393	OALLQHLLLL	KEOMROOKLL	VAGG--VPLH	POSPLATKERI	SPGIRG	THKLPRHRPLNRTO
HDAC9	393	OALLQHLLLL	KEOMROOKLL	VAGG--VPLH	POSPLATKERI	SPGIRG	THKLPRHRPLNRTO
HDAC4	411	SPLLQHMLV	LLEQPPAQAPL	VTGLGALPL	HAQS-LVGADR	VSP--SI	HKLROHRPLGRIO
HDRP	451	SAPLPQ--	STLAQLVI	OOOHOOFLEK	KOKO--YOOOI	HMNKLLSKS	IEOLKOPGSHLEAE
HDAC9a	451	SAPLPQ--	STLAQLVI	OOOHOOFLEK	KOKO--YOOOI	HMNKLLSKS	IEOLKOPGSHLEAE
HDAC9	451	SAPLPQ--	STLAQLVI	OOOHOOFLEK	KOKO--YOOOI	HMNKLLSKS	IEOLKOPGSHLEAE
HDAC4	467	SAPLPQNAQA	LIQHLLVIOO	HOOFLEKHK	KQOFQOOQL	QMNKIIPKPS	EPARQPEISHFEETIE
HDRP	507	EELQGDQAMO	EDRAPSSGNSTR	-SDSSACVDD	TLGOVGAVK	VEEPVDS	DEDAOIOEMES
HDAC9a	507	EELQGDQAMO	EDRAPSSGNSTR	-SDSSACVDD	TLGOVGAVK	VEEPVDS	DEDAOIOEMES
HDAC9	507	EELQGDQAMO	EDRAPSSGNSTR	-SDSSACVDD	TLGOVGAVK	VEEPVDS	DEDAOIOEMES
HDAC4	527	EELREHQAL	LDEPYLDR	LPQKEAHAQA	GVQVQKEP	LIESDEEEAE	PPREVEIPGQRQPSIEQ
HDRP	566	GEQAAFM	QOQVIGKDL	APGFVI	KVII-----	-----	-----
HDAC9a	566	GEQAAFM	QOQVIGKDL	APGFVI	KVII-----	-----	-----
HDAC9	566	GEQAAFM	QOQVIGKDL	APGFVI	KVII-----	-----	-----
HDAC4	587	ELLFRQQA	LLLEQQR	IHQLRNYQA	SMEAA	GIPVSFGCHRP	LSRAQSSPASATFFIVSVQEP

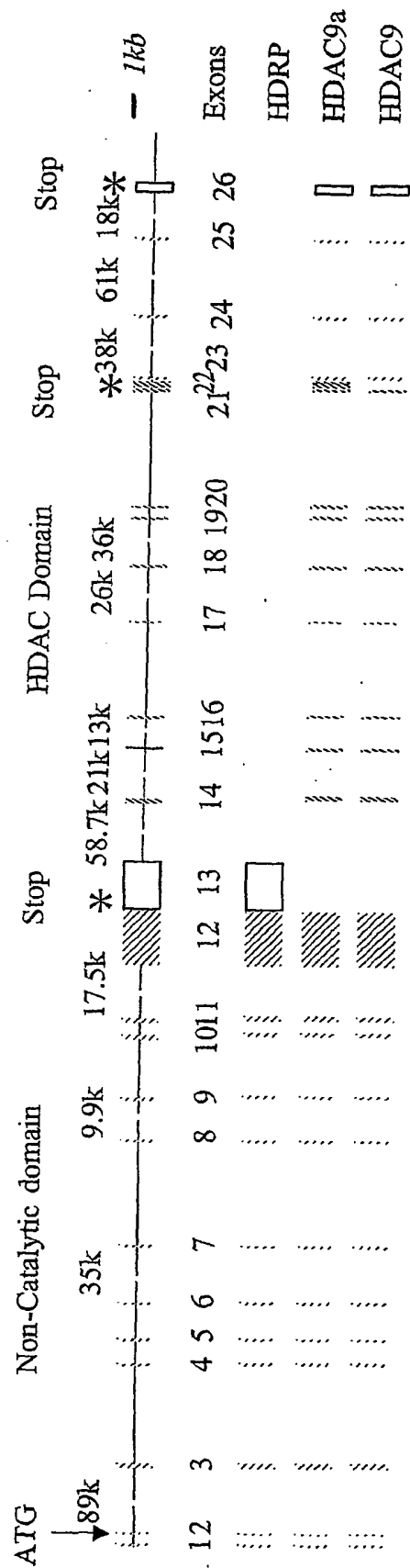
FIG. 3B

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HD RP	626	PLPGSATG	IA YD P L M L K H O C V C G N S T T H P E H A G R I O S I W S R L O E T G L L N K C E R I O G R K A
HD AC 9a	626	PLPGSATG	IA YD P L M L K H O C V C G N S T T H P E H A G R I O S I W S R L O E T G L L N K C E R I O G R K A
HD AC 9	647	ET R E R F T I T G L V Y D T L M L K H O C T C G S S S H P E H A G R I O S I W S R L O E T G L R G K C E I R G R K A	
HD AC 4			
HD RP	686	S L E E I O L V H S E H S L L Y G T N P L D G O K L D P R I L L G D D S O K F F S S L P C G G L G V D S D T I W N E L	
HD AC 9a	686	S L E E I O L V H S E H S L L Y G T N P L D G O K L D P R I L L G D D S O K F F S S L P C G G L G V D S D T I W N E L	
HD AC 9	707	T I L E E L O T V H S E A H T L L Y G T N P L N R O K L D S K L L G S I A S V E F V R - L P C G G V G V D S D T I W N E V	
HD AC 4			
HD RP	746	H S S G A A R M A V G C V I E L A S K V A S G E L K N G F A V V R P P G H H A E E S T A M G F C F F N S V A I T A K Y L	
HD AC 9a	746	H S S G A A R M A V G C V I E L A S K V A S G E L K N G F A V V R P P G H H A E E S T A M G F C F F N S V A I T A K Y L	
HD AC 9	766	H S A G A A R I A V G C V I E L V F K V A T G E L K N G F A V V R P P G H H A E E S T P M G F C F F N S V A V A K I L	
HD AC 4			
HD RP	806	R D O L N I S K I L I V D L D V H H G N G T O O A F Y A D P S I L Y I S L H R Y D E C N F F P G S G A P N E V R F I S L	
HD AC 9a	806	R D O L N I S K I L I V D L D V H H G N G T O O A F Y A D P S I L Y I S L H R Y D E C N F F P G S G A P N E V R F I S L	
HD AC 9	826	Q Q R L S V S K I L I V D W D V H H G N G T O O A F Y S D P S V L Y M S L H R Y D D G N F F P G S G A P D E V G T G P G	
HD AC 4			
HD RP	866	E P H F Y L Y L S G N C I T A	
HD AC 9a	866	E G Y N I N I A M I G G L D P P M G D V E Y L E A F R T I V K H V A K E F D P D M V L V S A G F D A I E G H T P P L G G	
HD AC 9	886	V G E N V N M A F T G G L D P P M G D A E Y L A A F R T I V M E I A S E F A P D M V L V S G G F D A V E G H P T P L G G	
HD AC 4			
HD RP	926	Y K V T A K C F G H L T K O L M T L A D G R V V L A L E G G H D L T A I C D A S E A C V N A L L G N E L E P L A E D I L	
HD AC 9a	946	Y N L S A R C F G Y L T K O L M G L A G G R I V L A L E G G H D L T A I C D A S E A C V S A L L G N E L D P L P E K V L	
HD AC 9			
HD AC 4			
HD RP	986	H Q S P N M N A V I S L O K I I E I O S M S L K F S	
HD AC 9a	1006	Q Q R E N A N A V R S M E K V M E I H S K Y W R C L Q R T T S T A G R S L I E A Q T C E N E E A E T V T A M A S L S V G	
HD AC 9			
HD AC 4			
HD RP	1066	V K P A E K R P D E E P M E E E P P L	
HD AC 9a			
HD AC 9			
HD AC 4			

FIG 3C

FIG. 3C



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FIG. 4

FIG. 5A
FIG. 5B
FIG. 5C
FIG. 5D

FIG. 5

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1 /¹ggggaagaga ggcacagaca cagataggag aagggcaccg gctggagcca cttgcaggac tgggggtttt tgcaacaaaa
ccctagcagc ctgaagaact

101 ctaagccag/²a tggggtggct ggacgagagc agctcttggc tcagcaaaaga ATGCACAGTA TGAICAGCTC AGT/³GGATGTG
AAGTCAGAAG TTCCTGTGGG

201 CCTGGAGCCC ATCTCACCTT TAGACCTAAG GACAGACCTC AGGATGATGA TGCCCCGTGGT GGACCCCTGTT GTCCGTGAGA
AGCAATTGCA GCAGGAATTA

301 CTTCCTATCC AGCAGCAGCA ACAATTCAG AACAGCTTC TGATAGCAGA GTTTCAGAAA CAGCATGAGA ACTTCACACG
GCAGCACCAG GCTCAGCTTC

401 AGGAGCATAT CAAG/⁴GAACTT CTAGCCATAA AACAGCAACA AGAACTCCTA GAAAGGAGC AGAAACTGGA GCAGCAGAGG
CAAGAACAGG AAGTAGAGAG

501 GCATCGCAGA GAACAGCAGC TTCTCTCTCT CAGAGGGCAAA GATAGAGGAC GAGAAAG /⁵GGC AGTGGCAAGT ACAGAAGTAA
AGCAGAAGCT TCAAGAGTTC

601 CTACTGAGTA AATCAGCAAC GAAACACACT CCAACTAATG GAAAAAATCA TTCCGTGAGC CGCCATCCCA AGCTCTGGA
CAGG/⁶GCTGCC CACCACACAT

701 CATGGATCA AAGCTCTCCA CCCCTTAGTG GAACATCTCC ATCCTACAAG TACACATTAC CAGGAGCACA AGATGCAAAG
GATGATTCC CCCTTCGAAA

FIG. 5A

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801 AACT/GCCTCT GAGCCCAACT TGAAGGTGG GTCCAGGTTA AAACAGAAAG TGGCAGAGAG GAGAAGCAGC CCCTTACTCA
GGCGGAAGGA TGGAAATGTT

901 GTCACCTTCAT TCAAGAAGCG AATGTTTGAG GTGACAG /⁸AAT CCTCAGTCAG TAGCAGTTCT CCAGGCTCTG GTCCAGTTT
ACCAACAAT GGGCCHACTG

1001 GAAGTGTAC TGAAAATGAG ACTTCGGTTT TGCCCCCTAC CCTTCATGCC GAG /⁹CAATGG TTTCACAGCA ACGCATTCTA
ATTGATGAG ATTCCATGAA

1101 CCTGTAACT CTTTATACCT CTCCTTCTTT GCCCAACATT ACCTTGGGGC TTCCCGGAGT GCCATCCCAG CTC AATG /¹⁰CTT
CGAATTCAT CAAAGAAAAG

1201 CAGAAGTGTG AGAGCGAGAC GCTTAGGCA GGTCTTCCTC TGCCTTGGCA GTATGGAGC AGCATCCCCG CATCTTCCAG
CCACCTCAT GTTACTTTAG

1301 AGGGAAGCC ACCCAACAGC AGCCACCAGG CTCCTCTGCA GCATTTATTA TTGAAAGAAC AATGCGACA GCAAAAGCTT
CTTGTAGCTG /¹¹ GTGGAGTTCC

1401 CTTACATCCT CAGTCTCCCT TGGCAACAAA AGAGAGAATT TCACCTGGCA TTAGAGGTAC CCACAAATTG CCCCCTCACA
GACCCCTGAA CCGAACCAG

1501 TCTGCACCTT TGCCTCAGAG CAGGTGGCT CAGCTGGTCA TTCAACAGCA ACACCAGCAA TTCTTGGAGA AGCAGAAGCA
ATACCAGCAG CAGATCCACA

1601 TGAACAAA /¹²CT GCTTTCGAAA TCTATTGAAC AACTGAAGCA ACCAGGCAGT CACCTTGAGG AAGCAGAGGA AGAGCTTCAG
GGGACCAGG CGATGCAGGA

FIG. 5B

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1701 AGACAGAGCG CCTCTAGTG GCAACAGCAC TAGGAGGGAC AGCAGTGCCT GTGTGGATGA CACACTGGGA CAAGTTGGGG
CTGTGAAGGT CAAGGAGAA

1801 CCACTGGACA GTGATGAAGA TGCTCAGATC CAGGAATGG AATCTGGGA GCAGGCTGCT TTTATGCAAC AG
/13GTAAVAGG CAAAGATTAA GCTCCAGGAT TTGTAATTAA AGTCATTATC TGA..... /14CCTTTCCT GGAACCCACG CACACACGTG

1901 CGCTCTCTGT GCGCCAAGCT CCGCTGGCTG CCGTTGGCAT GGATGGATTA GAGAAACACC GTCTGCTCTC CAGGACTCAC
TCTTCCCCCTG CTGCCTCTGT

2001 TTACCTCAC CCAGCAATGG ACCGCCCCCT CCAGCCTGGC TCTGCAACTG /15GAATTGCGCTA TGACCCCTTG ATGCTGAAAC
ACCAGTGGGT TTGTGGCAAT

2101 TCACACACC ACCCTGAGCA TECTGGACGA ATACAGAGTA TCTGCTCAG ACTGCAAGAA ACTGGGCTGC TAAATAAATG
TGAG/16CGAATT CAAGTGGAA

2201 AAGCCAGCCT GGAGGAATA CAGTTGTTC ATTCTGAACA TCACCTCCTG TTGTATGGCA CCAACCCCTT GGACGGACAG
AAGCTGGACC CCAGGATACT

2301 CCTAG/17GTGAT GACTCTCAAA AGTTTTTTC CTCATTACCT TGTTGGGAC TTGGG/18GTGGA CAGTGACACC ATTTGGGATG
AGCTACACTC GTCCGGTGCT

2401 GCACGCATGG CTGTTGGCTG TGTCAATCGAG CTGGCTTCCA AAGTGGCCTC AGGAGAGCTG AAGA /19ATGGGT TTGCTGTGTG
GAGGCCCCCT GGCCATCAG

2501 CTGAAGAATC CACAGCCATG /20GGGTCTGCT TTTTAAATTC AGTTGCAATT ACCGCCAAT ACTTGAGAGA CCAACTAAAT
ATAAGCAAGA TATTGATTGT

FIG. 5C

2601 AGATCTG/²¹GAT GTTCACCATG GAAACGGTAC CCAGCAGGCC TTTTATGCTG ACCCAGCAT CCTGTACATT TCACTCCATC
 GCTATGATGA AGGGAACTTT
 2701 TTCCCTGGCA GTGGAGCCCC AAATGAGG/²²TT CCGTTTATTT CTTTAGAGCC CCACTTTAT TTGTATCTTT CAGGTAATTG
CATTGCATGA ttacccttaa
 2801 ttttcttgtc ctttgcctggc gttttaaat acacgagatt actgaattgt cccatgggac caagaaccag tgcagaacaa
gtgcataacc cagagcactg
 2901 tttgtcaggg aaggttggc tgatttgatg tgtgtttga tgtttattc aagagctccc atgtgcttgt tttcctctct
tcttgcttc ttccatttgc
 3001 tctcttctct gccaccgtg gtgtgtctt ctctcccag /²³gttggaacag gccttggaagg aggtacaat ataaatattg
cctggacagg tggccttgat
 3101 cctcccatgg gagatgttga gtaccttga gcattcag/²⁴ga ccactgtgaa gcctgtggcc aaagagttg atccagacat
ggtcttaga tctgctggat
 3201 ttgatgcatt ggaaggccac accctctctc taggagggt caaagtgcg gcaaaatg/²⁵tt ttggtcattt gacgaagcaa
ttgatgacat tggctgatgg
 3301 acgtgtgggt ttggctctag aaggaggaca tgatctcaca gccatctgtg atgcatcaga agcctgtgta aatgccttc
taggaatga g/²⁶ctggagcca
 3401 cttgacagaag atattctcca ccaaagccc aatatgaatg ctgttatttc ttacagaag atcattgaaa ttcaaagtat
gtctttaag ttctcttaa....

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FIG. 5D

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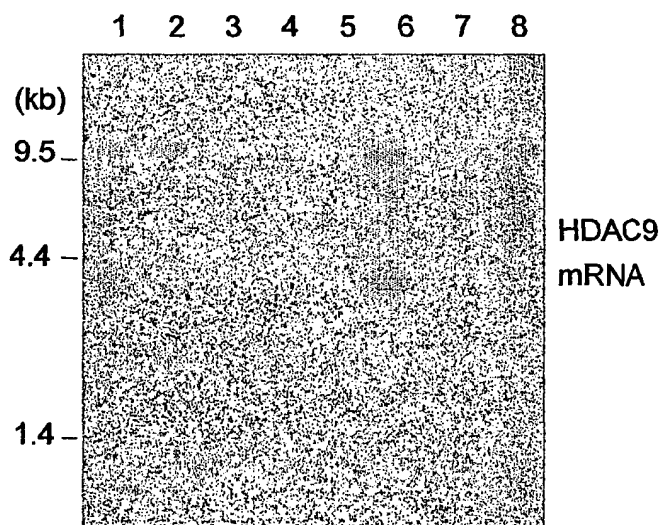


FIG. 6A

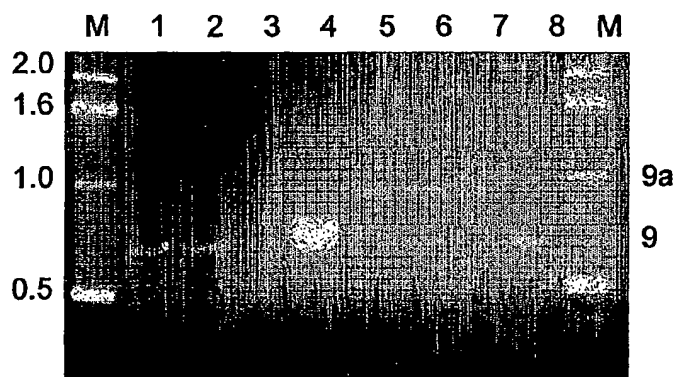


FIG. 6B

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BEST AVAILABLE COPY

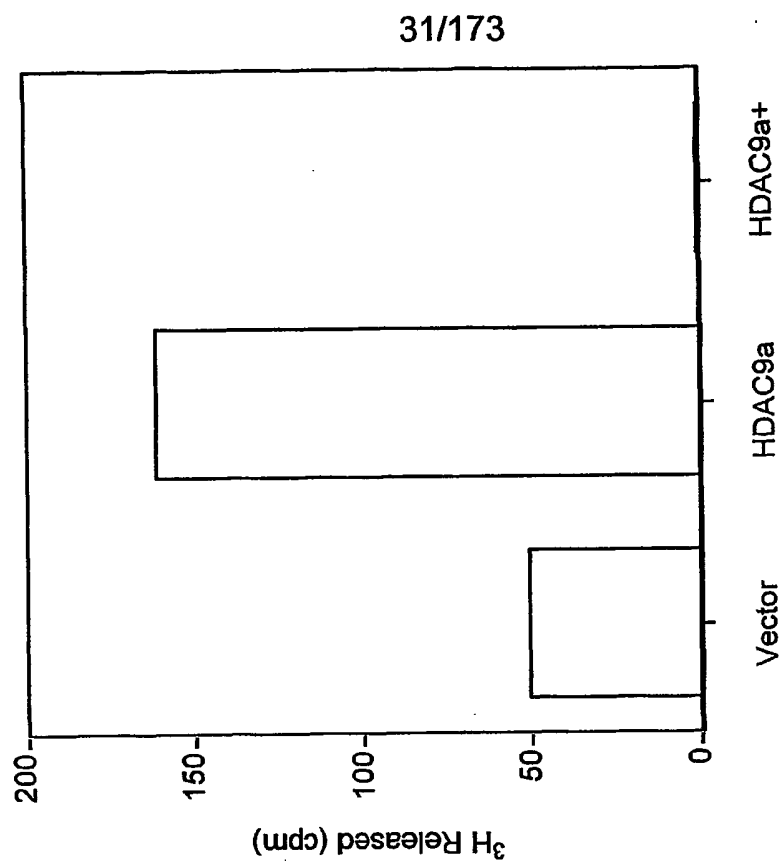


FIG. 8

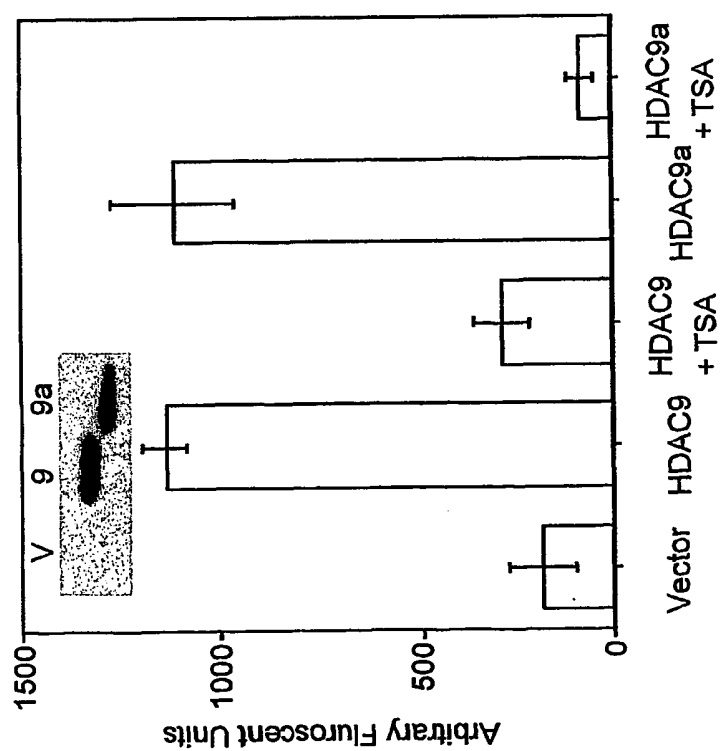


FIG. 7

FIG. 9A

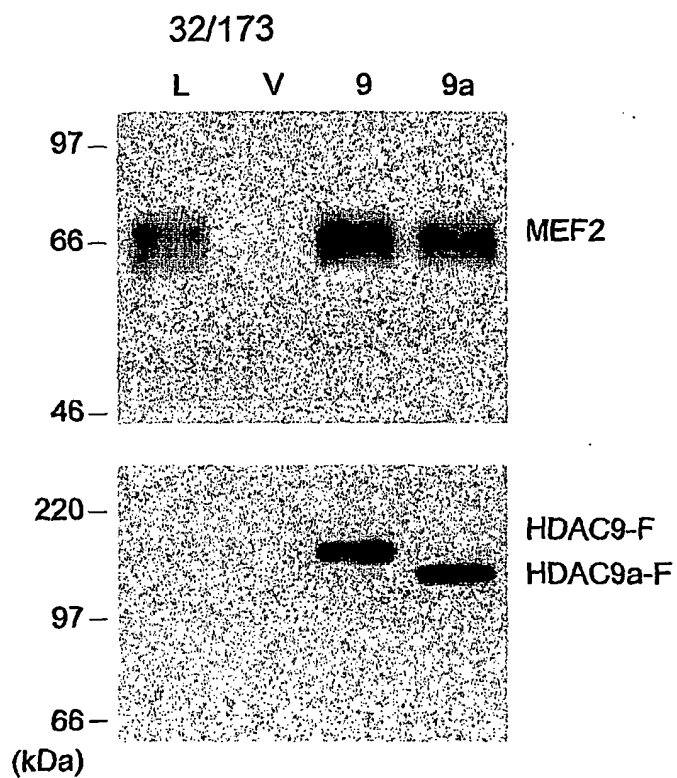
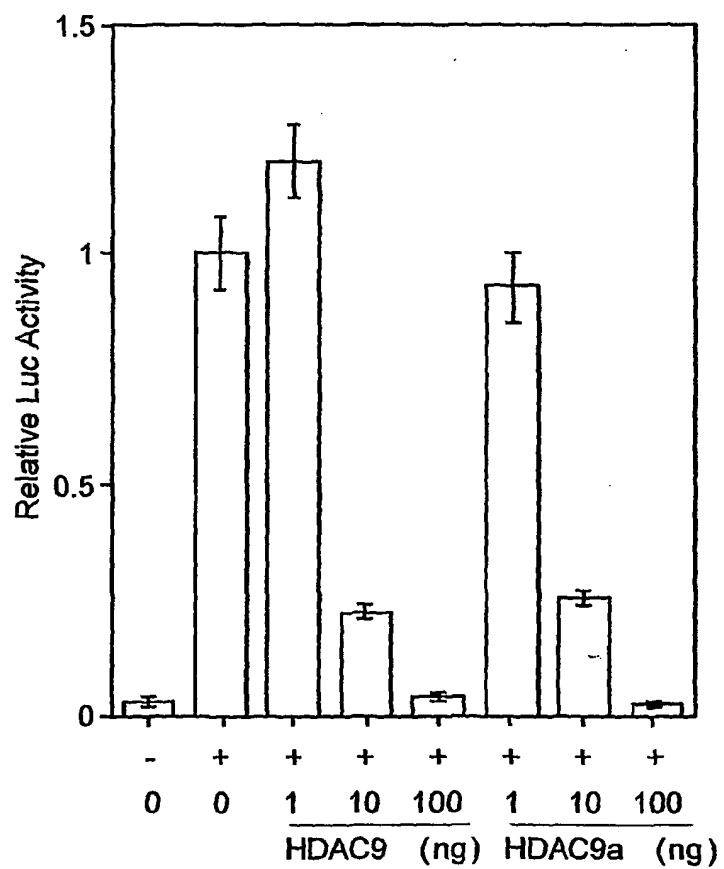


FIG. 9B



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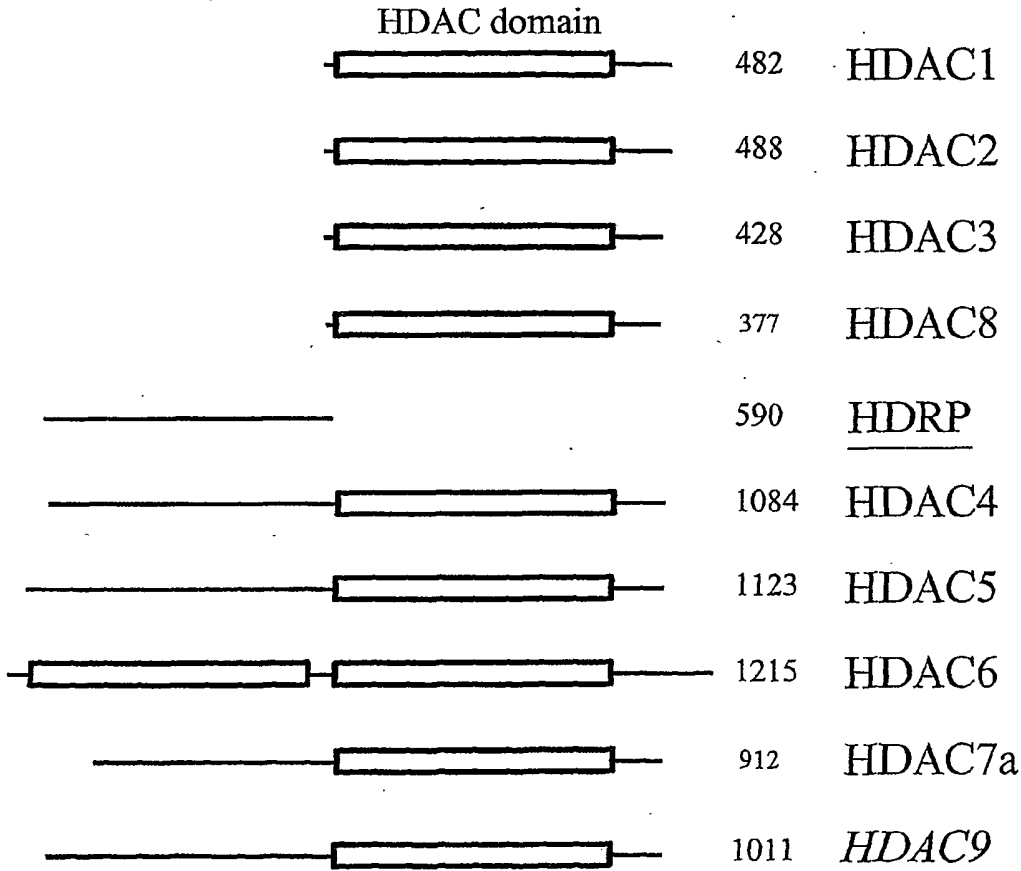


FIG. 10

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FIG. 11A
FIG. 11B
FIG. 11C
FIG. 11D
FIG. 11E
FIG. 11F

FIG. 11

FIG. 11A

cccattcgccattcaggctgcgaactggttggaaggcgcatcgggtggccctcttcgctattacgccagctggcgaaaggg
ggatgtgctgcaaggcgattaagtgggtaacgccagggtttccagtcacgacgttgtaaacgacggccagtgccaagct
gatctaataatattggccattagccatattattcattggttatatagcataaataatattggctattggccattgcatacgttgatcca
tatcataatatgtacatttatattggctcatgtccaacattaccgccatgttgacattgattattgactagttattaatagtaataatcag
gggtcattagttcatagcccatatatggagttccggttacataacttacgtaaatggcccgctggcgaccgccagcgaccc
ccgcccgttgacgtcaatagtgacgtatgttcccataagtaacgccaatagggactttccattgacgtcaatgggtggagtattacg

gtaactgccacttggcagtagacatcaagtgtatcatatgccaaagtcggccccctattgacgtcaatgacggtaaattggccgcct
 agcattatgccagtagacatgaccttacgggaggttctacttggcagtagacatctacgtattagtcacgtctattaccatgggtgatcg
 gtttggcagtagacacaaatggcgtgtagcgggttgactacgggatttccaaagtctccacccattgacgtcaatgggaggt
 tgtttggcaccaaaatcaacgggactttccaaaatgtcgaataacccccgggttgacgcaaatggcggttagcggtgtacg
 gtgggagggtctatataagcagagctcgttttagtgaaccgtcagaattcaagcttgcggccgcagatctatcgatctgcaggatc
 (EcoRV)
acc

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ATGCACAGTATGATCAGCTCAGTGGATGTGAAGTCAGAAAGTTCCCTGTGGG
 CCTGGAGCCCATCTCACCTTTAGACCTAAGGACAGACCTCAGGATGATGA
 TGCCCCGTGGTGACCCCTGTTGTCCGTGAGAAGCAATTGCAGCAGGAATTA
 CTTCTTATCCAGCAGCAGCAACAAATCCAGAAGCAGCTTCTGTATAGCAGA
 GTTTCAGAAACAGCATGAGAACTTGACACGGCAGCACCCAGGCTCAGCTTC
 AGGAGCATATCAAGGAACTTCTAGCCATAAAACAGCAACAAGAACTCCTA
 GAAAGGAGCAGAAACTGGAGCAGCAGAGGCAAGAAACAGGAAAGTAGAGAG
 GCATCGCAGAGAACAGCAGCTTCTCCTCTCAGAGGCAAGATAGAGGAC
 GAGAAAGGCGAGTGGCAAGTACAGAAAGTAAAGCAGAAAGCTTCAAGAGTTC
 CTA CTGAGTAAATCAGCAACGAAAGACACTCCAACTAATGGAAAAATCA
 TTCCGTGAGCCGCATCCCAAGCTCTGGTACACGGCTGCCACCCACACAT
 CATTGGATCAAGCTCTCCACCCCTTAGTGGAAACATCTCCATCCTACAAG

FIG. 11B

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TACACATTACCAGGAGCACAGATGCAAAAGGATGATTTCCTCCCTTCGAAA
AACTGCCCTCTGAGCCCAACTTGAAGTGCCTCAGGTTAAACAGAAAAG
TGGCAGAGAGAGAAAGCAGCCCTTACTCAGGCGAAGGATGGAAATGTT
GTCACTTCATTCAAGAAAGCGAATGTTTGAGGTGACAGAAATCCTCAGTCAG
TAGCAGTTCCTCAGGCTCTGGTCCAGTTCACCAAAACAATGGGCCAACTG
GAAGTGTTACTGAAAATGAGACTTCGGTTTTGCCCCCTACCCCTCATGCC
GAGCAAAATGGTTTTCACAGCAACGCAATCTAAATTCATGAAGATTCATGAA
CCTGCTAAGTCTTTATACCTCTCCTTCTTTGCCCCAACATTAACCTTGGGGC
TTCCCGCAGTGCCATCCCAGCTCAATGCTTCGAAATTCACCTCAAGAAAAG
CAGAAAGTGTGAGACGCAGACGCTTAGGCAAGGTGTTCTCTGCTGCCCTGGGCA
GTATGGAGGCAGCATCCCGGCATCTTCAGCCACCTCATGTACTTTAG
AGGAAAGCCACCCACAGCAGCCACAGGCTCTCCTGCAGCATTTATTA
TTGAAAGAACAATGCGACAGCAAAAAGCTTCTTGTAGCTGGTGGAGTTCC
CTTACATCCTCAGTCTCCCTTGGCAACAAGAGAGAAATTCACCTGGCA
TTAGAGGTACCCACAAATTGCCCGCTCACAGACCCCTGAACCGAACCCAG
TCTGCACCTTTGCCCTCAGAGCACGTTGGCTCAGCTGGTCAATTCACACAGCA
ACACAGCAATCTTGGAGAAAGCAGAAAGCAATACCAAGCAGCAGATCCACA
TGAACAAACTGCTTTTCGAAATCTATTGAACAACTGAAGCAACAGGCAGT
CACCTTGAGGAAGCAGAGGAAGAGCTTCAGGGGGACCAAGCGATGCAGGA
AGACAGAGCGCCCTCTAGTGGCAACAGCACTAGGAGCGACAGCAGTGCTT
GTGTGGATGACACACTGGGACAAAGTTGGGGCTGTGAAGGTCAAGGAGGAA
CCAGTGGACAGTGATGAAGATGCTCAGATCCAGGAAATGGAATCTGGGGA
GCAGGCTGCTTTTATGCAACAGCCTTCTCTGGAACCCACGCACACACGTG
CGCTCTCTGTGCGCCAAAGCTCCGCTGGCTGGCTGGCATGGATGGATTATTA

FIG. 11C

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GAGAAACACCGTCTCGTCTCCAGGACTCACTCTTCCCTGCTGCCCTCTGT
TTTACCTCACCAGCAATGGACCGCCCCCTCCAGCCTGGCTCTGCAACTG
GAATTGCCCTATGACCCCTTGATGCTGAAACACCAGTCCGTTTGTGGCAAT
TCCACCACCACCCCTGAGCATGCTGGACGAATACAGAGTATCTGGTCACG
ACTGCAAGAAACTGGGCTGCTAAATAAATGTGAGCGAAATTC AAGGTCGAA
AAGCCAGCCTGGAGGAAATACAGCTTGTTTCTGAAACATCACTCACTG
TTGTATGGCACCAACCCCTGGACGGACAGAAAGCTGGACCCAGGATACT
CCTAGGTGATGACTCTCAAAAGTTTTTTTCTCTATTACCTTGTGGTGGAC
TTGGGGTGGACAGTGACACCAATTTGGAATGAGCTACACTCGTCCGGTGCT
GCACGCATGGCTGTTGGCTGTGTCTCATCGAGCTGGCTTCCAAAGTGGCCCTC
AGGAGAGCTGAAGAAATGGGTTTGTGTTGTGAGGCCCCCTGGCCATCACG
CTGAAGAAATCCACAGCCAATGGGGTTCTGCTTTTAAATTCAGTTGCAATT
ACCGCCAAATACTTGAGAGACCAACTAAATAATAAGCAAGATAATTGATTGT
AGATCTGGATGTTACCATGGAAACGGTACCAGCAGGCCCTTTTATGCTG
ACCCAGCATCCTGTACATTTCACTCCATCCGCTATGATGAAGGAACTTT
TTCCCTGGCAGTGGAGCCCCAAATGAGGTTGGAACAGGCCCTTGGAGAAGG
GTACAATATAAATATTGCTGGACAGGTGGCCTTGATCCTCCCATGGGAG
ATGTTGAGTACCTTGAAGCATTCAGGAccaTCGTGAAGCCTGTGGCCAAA
GAGTTTGATCCAGACATGGTCTTAGTATCTGCTGGATTTGATGCATTGGA
AGGCCACACCCCTCCTAGGAGGTACAAAGTGACGGCAAAATGTTTGTG
GTCATTTGACGAAGCAATTGATGACATTGGCTGATGGACGTTGTGTGTG
GCTCTAGAAGGAGGACATGATCTCACAGCCATCTGTGATGCATCAGAAGC
CTGTGTAATGCCCTTCTAGGAAATGAGCTGAGCCACTTGCAGAAAGATA
TTCTCCACCAAGCCCCGAATATGAATGCTGTTATTCTTTTACAGAAGATC
ATTGAAATTCAAAAGTATGTCTTTAAAGTTCTCT

FIG. 11D

FIG. 11E

[illegible]

[illegible]

FIG. 11F

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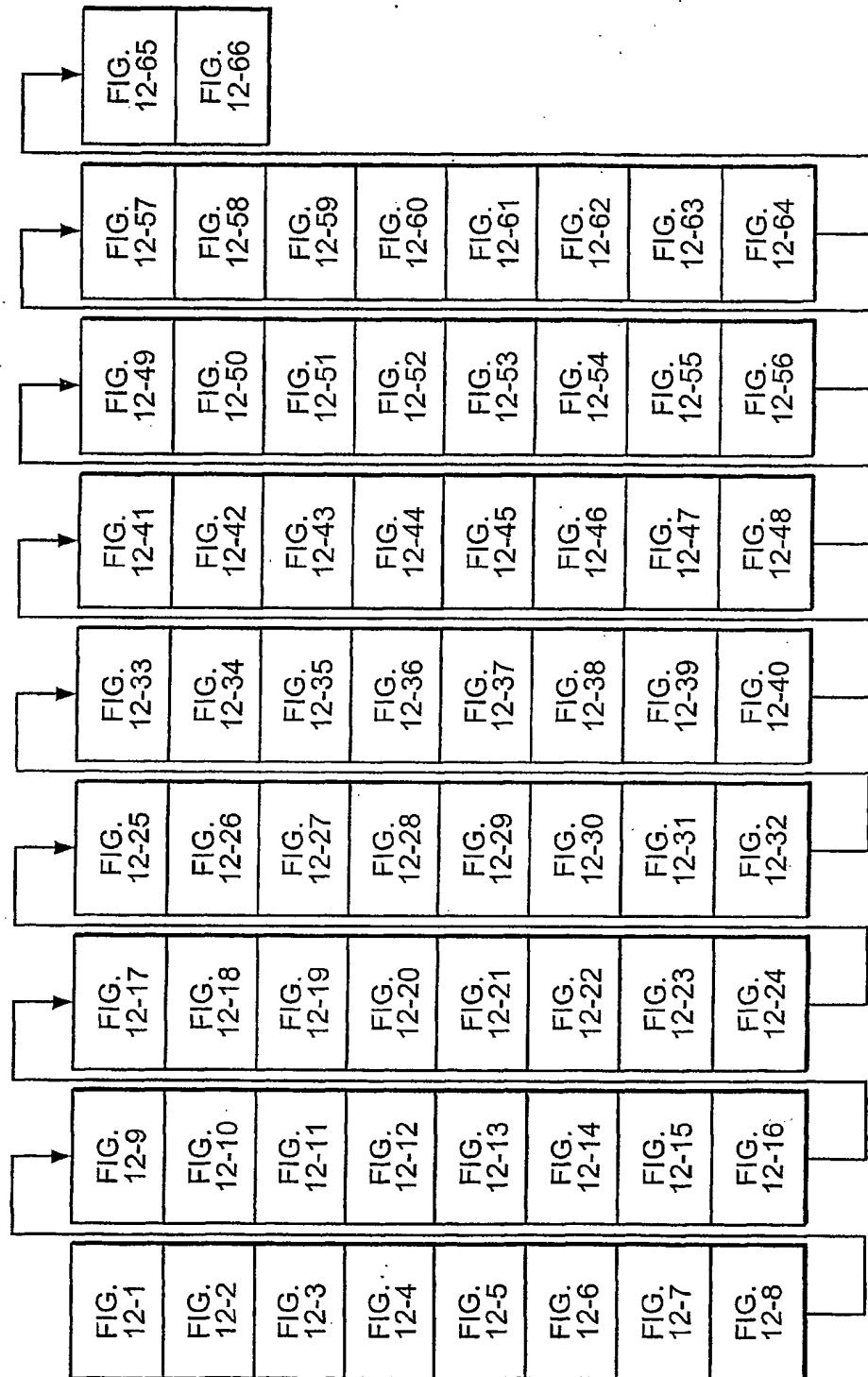


FIG. 12

pFLAG-CMV-5b-HDAC9

7699 base pairs

Graphic map | Table by enzyme name

	BstMCI				
AviII	PvuI BsiEI	EarI	MspAII		
BglI FspI	BsaOI	Eam1104I	PvuII		
cccatcgcattcaggctgcgcaactgttgggaaggcgatcggtgcgggcctcttcgctattacgccagctgg					
base pairs					
gggtaagcggtaagtccgacgcgttgacaaccccttcccgcctagccacgcccggagaagcgataatgcggtcgacc					
1 to 75					41/173
	Acc16I	BspCI	Ksp632I	NspBII	
		Bsh1285I			
		Ple19I			

cgaagggggatgtgctgcaaggcgattaagtgggtaacgcccagggtttcccagtcacgacgttgtaaacg
base pairs
gcttccccctacacgacgttccgcctaattcaaccattgcgggtcccaaaagggtcagtgctgcaacatttgc
76 to 150

FIG. 12-1

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	MSCI	
	CfrI	
	SspI MluNI	
EaeI		
acggccagtgccaagctgatctaataatcaataattggccattagccataattattcattggttatatagcataaaatcaa		
base pairs		
tgccggtcacgggttcgactagattagttataaaccggtaatcgggtataataagtaaccaataatatcgtatttagtt		
151 to 225		
CfrI	EaeI	
	Bali	
	MSCI	
	MluNI	
SspI	EaeI	SspBI
	BsrDI	Bsp1407I
tattgggtattggccattgcatatcggtgtatccatatcataaataatgtacatttatatttggtcatgtccaaacatt		
base pairs		
ataaccgataaaccggtaacgtatgcaacatagggtatagttatatcatgtataataaccgagtagcaggttgtaa		
226 to 300		
CfrI		BsrGI
	Bali	

FIG. 12-2

	HincII	SpeI	VspI	PshBI
accgccatgttgacattgattattgactagttattaatagtaataatcaattacggggtcatttagttcatagcccata				
base pairs				
tggcggtaacaactgtaactaataactgatcaataattatcattagttaatgccccagtaatacaagtatcgggtat				
301 to 375				
	HindII	AclNI	AsnI	AseI

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	HinII	BstMCI	ACYI	HincII
tatggagttccggttacataacttacggtaaatggcccgccctggcgaccgccccagcgacccccgcttgacg				
base pairs		BglI	BsaOI	
atacctcaaggcgcaatgtattgaatgccatttaccggcggaaccgctggcggggtcgctggggcgggcaactgc				
376 to 450				
	HindII	Bsh1285I	BsiEI	

FIG. 12-3

AatII
 BbiII
 tcaatagtgacgtatgttcccatagtaacgccaataggactttccattgacgtcaatgggtggagtatttacgg
 base pairs
 agttatcactgcatacaagggtatcattgcggttatccctgaaaggtaactgcagttacccacctcataaatgcc
 451 to 525
 Hsp92I
 Msp17I
 BsaHI
 Hsp92I
 44/173
 BglI
 NdeI
 BbiII
 HinII
 AciI AatII
 taaactgcccacttggcagtagcatcaagtgtatcatatgccaaagtcgccccctattgacgtcaatgacggtaaa
 base pairs
 atttgacgggtgaaccgtcatgtagttcacatagtagtgcaggggggataaactgcagttactgccattt
 526 to 600
 FauNDI
 Msp17I
 BsaHI
 Hsp92I

FIG. 12-4

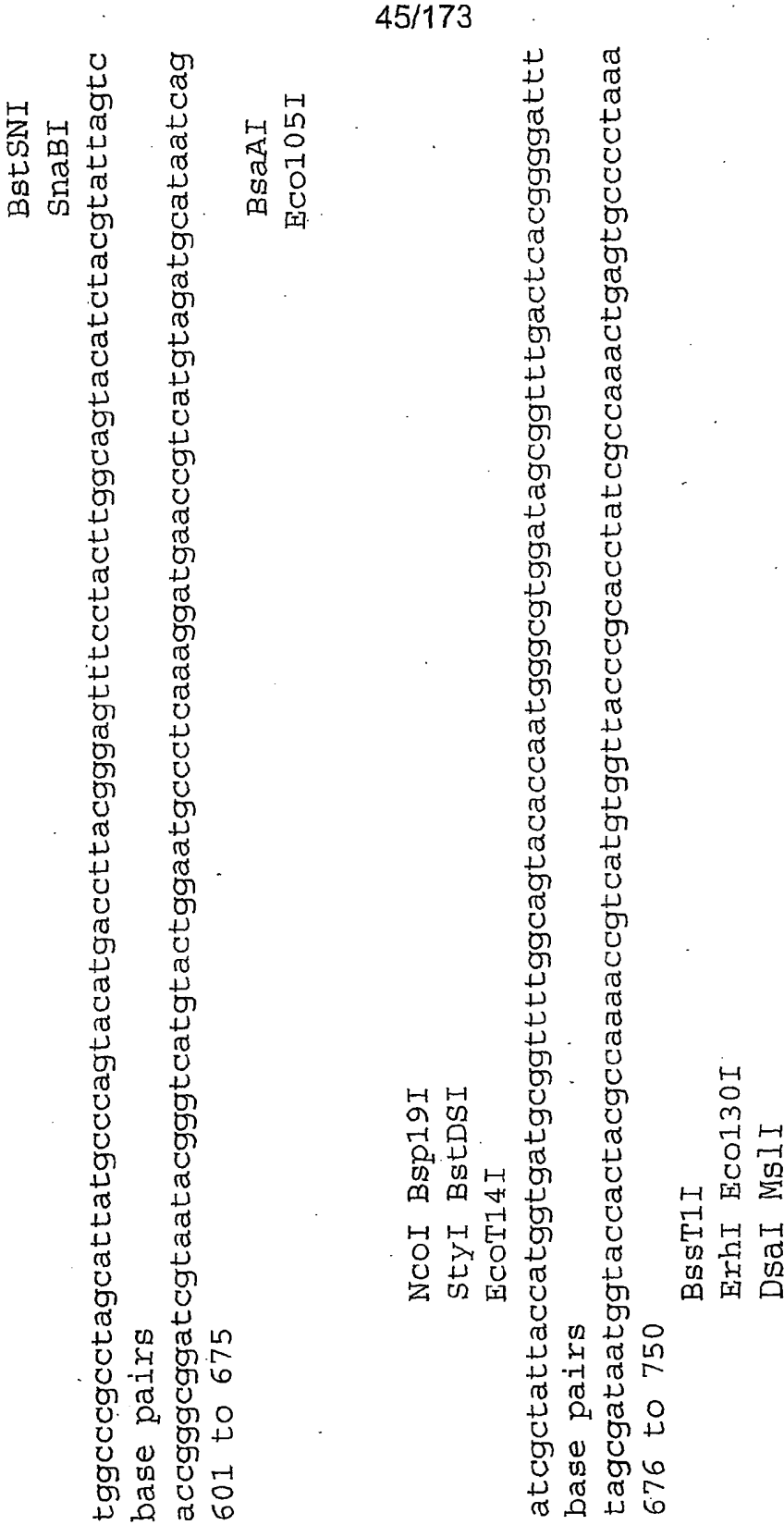


FIG. 12-5

BbiII
 HincII
 AcyI AatII
 AccB1I
 BshNI
 ccaagtctccacccattgacgtcaatgggagttgttttggcaccaaaaatcaacgggactttccaaaatgtcgt
 base pairs
 ggttcagaggtgggtaactgcagttaccctcaacaaaaccgtggttttagttgcccctgaaagggttttacagca
 751 to 825
 Msp17I
 BsaHI
 Hsp92I
 BanI
 Eco64I
 46/173
 HincII
 aataacccccccgttgacgcgcaaatgggcggtagcggtgtacggtgggaggtctatataaagcagagctcgttta
 base pairs
 ttattgggcggggcaactgcggtttaccggccatccgcacatgccaccctccagatatattcgtctcgagcaaat
 826 to 900
 HindII
 Eco24I
 EcoICRI
 BanII
 Ecl136II
 SacI

FIG. 12-6

FriOI
 SstI
 BsiHKA
 Bbv12I
 AcsI
 ApoI
 AspHI
 gtgaaccgtcagaattcaagcttgccgcagatctatcgatctgcaggatatcaccatgcacagtatgacg
 base pairs
 cacttggcagctcttaagttcgaaacggcgctctagatagtagacgtcctatagtggtacgtgtcatatgacg
 901 to 975
 Psp124BI
 EcoRI
 Alw21I
 47/173
 EaeI
 CfrI
 NotI
 BglII
 BscI
 XhoII
 BspXI
 BstSFI
 BseCI
 ClaI
 Bsp106I
 BclI
 Ksp22I
 CviOI
 Eco24I
 BpmI
 CvnI
 AocI
 Bsu36I
 Bsu36I
 ctcagtggatgtgaagtcagaagttcctgtgggctggagcccatctcacctttagaccctaaggacagacacacg
 base pairs
 gagtcacctacacttcagttcctcaaggacacccggacccctcggttagagtggaatctggattcctgtctggagtc
 976 to 1050
 GsuI
 BanII
 Eco81I
 Bse21I
 Eco81I
 Bse21I

FIG. 12-7

gatgatgatgccccgtggtggaccctgttgccgtgagaagcaattgcagcaggaattacttcttatccagcagca
base pairs
ctactactacgggcaccacacctgggacacaggcactcttcgttaacgtcgtccttaataatgaagaataggtcgtcgt
1051 to 1125

DsaI DrrI MfeI Asp700I
BstDSI MunI XmnI

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FIG. 12-8

AlwNI
 gcaacaaatccagaagcagcttctgtatgacagagtttcagaacacagcatgagaacttgacacggcagcaccaggc
 base pairs
 cgttggttaggtcttcgtcgaagactatcgtctcaaaagtcttctgtcgactcttgaactgtgccgtcgtggtccg
 1126 to 1200

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BlpI	Eco57I	EcoNI	AlwNI
CellII			
tcagcttcaggagcatatcaaggaaacttctagccataaaacagcaacaagaactcctagaaaaggagcagaaact			
base pairs			
agtcgaagtcctcgtatagttcccttgaagatcgggtattttgtcgttggttcttgaggatctttcctcgtctttga			
1201 to 1275			
Bsp1720I			
Bpu1102I			

FIG. 12-9

BpmI
ggagcagcagaggcaagaacagggaagtagagaggcatcgagagaaacagcagcttcctcctctcagagggcaaaaga
base pairs
cctcgtcgtctccggttcttggtccttcattcctccgtagcgtctctgtcgtcgaaggaggagagtcctccggtttct
1276 to 1350
GsuI

50/173

EcoNI

HindIII
tagaggacgagaaaaggcagtggaagtagacagaagtaaaagcag aagcttcaagagttcctactgagtaaatcagc
base pairs
atctcctgctctttcccggtcacccgttcattgtcttcatttcgtc ttcgaaagttctcaaggatgactcatttagtcg
1351 to 1425

FIG. 12-10

Van91I	Van91I	
AccB7I	AccB7I	
aacgaaagacactccaactaatggaaaaaatcattccgtgagccgccatcccaagctctggtacacggctgcccc		
base pairs		
ttgcttttctgtgaggttgattaccttttttagtaaggcactcggcggtagggttcgcagaccatgtgccgacgggt		
1426 to 1500		
Esp1396I	Esp1396I	51/173
PflMI	PflMI	

ccacacatcattggatcaaagctctccacccttagtggaacatctccatcctacaagtacacattaccaggagc	
base pairs	
ggtgtgtagtaacctagtttcgagaggtggggaatcaccttgtagaggtaggatgttcattgtgtaatgggtcctcg	
1501 to 1575	

FIG. 12-11

52/173

Alw21I	BstBI		
AspHI	Bpu14I	FriOI	
	Csp45I	Eco24I	
acaagatgcaaaggatgatttcccccttcgaaaaactgcctctgagcccaacttgaaggcggtccagggttaaa			
base pairs			
tggttctacgtttcctactaaaggggaagctttttgacggagactcggggttgaacttccacgccagggtccaattt			
1576 to 1650			
BsiHKAI	SfuI	Bsp119I	BanII
Bbv12I	NspV		
	LspI		
	BseRI	EcoNI	
acagaaaagtggcagagaggagaagcagcccccttactcagggcgaaggatggaaatgttgtcacttcattcaagaa			
base pairs			
tgtctttcaccgctctctcctctctcgtcgggggaatgagtcgcgccttcctacctttacaacagtgaaagtaagttctt			
1651 to 1725			

FIG. 12-12

Van91I	Van91I
AccB7I	AccB7I
BpmI PflMI	
gcgaatgttgaggtagacagaatcctcagtcagtagcagttctccaggctctggtcccagttcaccaacaatgg	
base pairs	
cgcttacaaactccactgtcttaggagtcagtcacgtcaagaggtccgagaccagggtcaagtggtttgttacc	
1726 to 1800	
GsuI	Esp1396I
Esp1396I	PflMI
AlwNI	

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gccaaactggaagtgttactgaaaatgagacttcggtttgccccctacccctcatgccgagcaaatggtttcaca

base pairs

cggttgaccttcacaatgacttttactctgaagcccaaacgggggatggggagtagcggctcgtttaccaaaagtgt

1801 to 1875

FIG. 12-13

BsaMI
Mva1269I
gcaacgcatttctaattcatgaagattccatgaacctgtaagtctttatacctctccttcttggcccaacattac
base pairs
cggtgcgtaagattaagtacttctaagggtacttggacgattcagaaatatggagaggaagaaacggggttgtaatg
1876 to 1950
BsmI RcaI
BspHI

BspMI
XcmI

54/173

ErhI
BssT1I
cttgggggttcccgcagtgccatcccagctcaatgcttcgaattcactcaagagaaaagcagaagtgtgagacgca
base pairs
gaaccccgaaagggcggtcacggtagggtcgagttacgaagcttaagtgaagtcttcttttcgtcttcacactctgcgt
1951 to 2025
EcoT14I
SfuI Bsp119I
BsmBI
StyI
Eco130I
NspV ApoI
LspI EcoRI

FIG. 12-14

55/173

MsI I
gacgcttaggcaaggtgttcctctgtcctgggcagtagtgaggcagcatcccgcatctccagccaccctcatgt
base pairs
ctgcgaatccgttccacaaggagacggaccggtcatacctccgtcgtagggccgtagaaggtcggtgggagtaca
2026 to 2100

Pst I
Sfi I
tactttagggaaagccaccaccaacagcagcaccaggctctc ctgcagcatttattattgaaagaacaaatgcg
base pairs
atgaaatctcccttttcggtgggtgtcgtcgggtccgagag gacgtcgtaaataaactttcttgtttacgc
2101 to 2175
BstSFI

FIG. 12-15

Eco130I
 StyI
 EcoT14I
 Apol
 HindIII
 acagcaaaagcttctttagctgggtggagttcccttacatcctcagtcctcccttggcaacaaagagagaatttc
 base pairs
 tgtcgttttcgaagaacatcgaccacctcaagggaatgtaggagtcagaggggaaccgttggtttctctcttaaag
 2176 to 2250
 Bst1I
 ErhI
 AcsI
 Asp718I
 Acc65I
 BshNI
 BsgI
 acctggcattagagggtaccacaaaattgccccgtcacagacccctgaaccgaaccagtcctgcacctttgcctca
 base pairs
 tggaccgtaatctccatgggtgtttaacggggcagtgctctggggacttggcttgggtcagacgtggaaacggagt
 2251 to 2325
 BanI
 KpnI
 AccB1I
 Eco64I

56/173

FIG. 12-16

57/173

Bpu1102I
 Alw21I Bsp1720I
 AspHI CelII
 gagcacgttggctcagctggtcattcaacagcaacaccagcaattcttggagaagcagaagaataaccagcagca
 base pairs
 ctctgtgcaaccgagtcgaccagtaagtgtcggtggtcggttaagaacctcttcgtcttcggttatgggtcgtcgt
 2326 to 2400
 BsiHKAI PvuII
 Bbv12I B1pI MspA1I
 NspBII
 MflI
 XhoII
 gatccacatgaacaaactgcttttcgaaatctattgaacaaactgaagcaaccaggcagtcaccttgaggaagcaga
 base pairs
 ctagggtgacttggttgacgaaaagctttagataaacttggtgacttcggttggtccgtcagtggaactccttcgtct
 2401 to 2475
 BstYI
 BstX2I
 SfuI Bsp119I
 NspV
 LspI

FIG. 12-17

58/173

EarI
 Eam1104I
 Asp700I
 Bbv16II
 BbsI Bsp143II
 ggaagagcttcaggggaccaggcgatgcaggaagacagagcgccctctagtggcaacagcactaggagcgacag
 base pairs
 ccttctcgaagtcctccctgggtccgctacgtccttctgtctcgcgggagatcacccgttgctcgtgatccctcgctgtc
 2476 to 2550

XmnI Eco57I
 Ksp632I
 SspI
 BpiI HaeII
 BpuAI BstH2I

BcgI
 cagtgccttggtggatgacacactgggacaagtggggctgtgaagggtcaaggaggaaaccagtggaacagtgatga
 base pairs
 gtcacgaaacacacctactgtgtgacctgttcaacccccgacacttccagttcctccttggtcacctgtcactact
 2551 to 2625

FIG. 12-18

MflI Van91I
 XhoII AccB7I
 agatgctcagatccaggaaatggaatctggggagcaggctgcttttatgcaacagcctttccttggaacccacgca
 base pairs
 tctacgagtcctaggtcctttaccttagacccctcgccgacgaaatacgttgctcgaaaggaccttgggtgcgt
 2626 to 2700

BstYI Esp1396I
 BstX2I PflMI

59/173

PmaCI
 PmlI
 AflIII

NspBII

Esp3I

cacacgtgcgctctctgtgcgccaagctccgctggctgcggttgccatggatggattagagaaacaccgtctcgt
 base pairs
 gtgtgcacgcgagagacacgcggttcgaggcgaccgacgccaaccgtacctaatctcttggcagagca
 2701 to 2775

MslI Eco72I

MspAII

BsmBI

BsaAI
 BbrPI

FIG. 12-19

60/173

	EarI		BsrDI	BpmI
	Eam1104I			
ctccaggactcactcttccccctgctgcctctgtttacctcaccagcaatggacccgccccctccagcctggctc				
base pairs				
gaggtcctgagtgagaaggggacgacggagacaaaaatggagtgggtcgttacctggcgggggaggtcggaccgag				
2776 to 2850				
GsuI	Ksp632I			GsuI

	XcmI
tgcaactggaattgccttatgaccccttgatgctgaaacaccagtgcggttgtggcaattccaccaccacctga	
base pairs	
acgttgaccttaacggatactggggaaactacgactttgtggtcacgcaaacacacgttaagggtgggtgggact	
2851 to 2925	

FIG. 12-20

sphI
 BbuI
 gcattgctggacgaatacacagagtatctggtcacgactgcaagaaactggggctgctaataaatgtgagc gaattca
 base pairs
 cgtagacactgcttatgtctcatagaccagtgctgacgttctttgacccgacgattttattacactcg cttaaagt
 2926 to 3000
 PaeI
 NspI
 AcsI
 ApsI
 EcoRI

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AggTCGAAAAGCCAGCCTGGAGGAAATACAGCTTGTTcattctgaacatcactcactgttgatggcaccaaccc
base pairs
tccagcttttcggtcggacctcctttatgtcgaacaagtaagactttagtgagtgaacaacataccgtggttg999
3001 to 3075

BpmI
AccB1I
BshNI
BanI
Eco64I
GsuI

FIG. 12-21

62/173

ErhI
StyI Eco130I
EcoT14I
BstXI AlwNI
cctggacggacagaagctggaccccaggataactcctaggtgatgactctcaaaagttttttccctcattaccttg
base pairs
ggacctgcctgtcttcgacctggggtcctatgaggatccactactgagagttttcaaaaaaggagtaaatggaac
3076 to 3150

BstT1I
AvtII
BlnI

BsaWI BsgI
tggaggacttggggtggacagtgacaccatttgggaatgagctacactcgctccggtgctgcacgcatgggctgttg
base pairs
accacctgaacccacacctgtcactgtggtaaaccttactcgatgtgagcaggccacgacgtgcgtaccgacaacc
3151 to 3225

FIG. 12-22

CvnI	CfrI
AocI	DraII EaeI
Bsu36I	Eco57I

ctgtgtcatcgagctggcttccaaagtggcctcaggagagctgaagaatgggtttgctgttgtagggccccctgg
base pairs
gacacagtagctcgaccgaaggtttcaccggagtcctctcgacttcttaccacaaacgacaacactccgggggacc
3226 to 3300

Eco81I	EcoO109I
Bse21I	

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MscI	ErhI Ecol30I
	BstXI
	Eco57I MslI DsaI

ccatcacgctgaagaatccacagccatgggttctgtcttttaattcagttgcaattaccgccaatacttgag
base pairs
ggtagtgcgacttcttaggtgtcgggtaccccaagacgaaaaaattaagtcaacgtaatggcggttatgaactc
3301 to 3375

MluNI	EcoT14I
BalI	StyI BstDSI
	NcoI Bsp19I

FIG. 12-23

BstX2I NcoI Bsp19I Asp718I SseBI
 BstYI StyI BstDSI AccB1I
 Eco147I
 BsaI XhoII EcoT14I BshNI StuI
 agaccaactaaataagcaagatatgtattgtagatctggatgttcaccatggaaacggtaccagcaggcctt
 base pairs
 tctggttgatttatattcgttctataaactaacatctagacctacaagtgggtacctttgccatgggtcggtccggaa
 3376 to 3450
 Eco31I BglII BssT1I Bani KpnI AatI
 MflI ErhI Eco130I Eco64I Pme55I
 DsaI Acc65I

64/173

SspBI Bsp1407I MslI Asp700I
 ttatgctgacccagcatcctgtacatttcactccatcgctatgatgaagggaactttttccctggcagtgaggc
 base pairs
 aatacgactggggtcgtaggacatgtaaagtgaggtagcgatactacttcccttgaaaaaggacccgtcacctcg
 3451 to 3525
 BsrGI XmnI

FIG. 12-24

<p> FriOI Eco24I cccaaatgaggttggaacaggccttggaagggtacaataataattgcctggacaggtggccttgatcctcc base pairs gggtttactccaaccttgtcgggaacctcttcccatgttatattataaaggacctgtccaccggaactaggagg 3526 to 3600 BanII AatI StyI Pme55I Eco130I EcoT14I </p>	<p> SseBI ErhI Eco147I StuI BssT1I SspI </p>
<p> NcoI Bsp19I StyI BstDSI EcoT14I </p>	<p> 65/173 MscI MluNI AspI MscI MluNI EaeI Mva1269I BsaMI EaeI AtsI </p>
<p> catgggatgttgagtaccttgaagcattcaggaccattcgtgaagcctgtggccaaagagtttgatccagacat base pairs gtacctctacaactcatggaacttcgtaagtcctggtagcacttcggacacccgggttctcaaaactaggctgta 3601 to 3675 BssT1I DsaI ErhI Eco130I </p>	<p> CfrI Tth111I BsmI CfrI BalI </p>

FIG. 12-25

66/173

Mph1103I
 EcoT22I
 Ppu10I
 EconI
 ggcttagtatctgctggatttgatgcattggaaggccacacccctcctctaggagggtacaaagtgacggcaaa
 base pairs
 ccagaatcatagacgacctaactacgtaaccttcgggtgtgggaggagatcctcccatgtttcactgccggttt
 3676 to 3750

NsiI
 Zsp2I
 BseRI

MfeI
 AflIII
 XbaI
 atgttttggtcatttgacgaagcaattgatgacattggctgatggacgtgtggttggctctagaaggaggaca
 base pairs
 tacaataaccagtaactgcttcgtaactactgtaaccgactacctgcacacacacacacagagatcttcctcctgt
 3751 to 3825

MunI

FIG. 12-26

Mph1103I
 EcoT22I
 Ppu10I
 BpmI
 tgatctcacagccatctgtgatgcatacagaagcctgtgtgtaaatgcccttctaggaaatgagctggagccacttgc
 base pairs
 actagagtgtcggtagacactacgtagtcttcggacacatttacgggaagatcccttactcgacctcgggtgaacg
 3826 to 3900
 NsiI
 Zsp2I
 GsuI
 67/173
 Asp700I
 BsaMI
 Mva1269I
 ApoI
 agaagatatctctccaccaaaagccgaatatgaatgctgttattctttacagaagatcattgaaaattcaaagtat
 base pairs
 tcttctataagaggtggttcgggcttatacttacgacaataaaagaaatgtcttctagtaactttaagttcata
 3901 to 3975
 XmnI
 BsmI
 AclI

FIG. 12-27

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Eco130I
 StyI
 EcoT14I
 GsuI
 MslI
 Bst1I
 BpmI
 ErhI

FIG. 12-28

BcoI
 Ama87I
 BcgI
 AvaI
 tggctcactgcaatctccgcctcctgggttcaagcgattctcctgcctcagcctcccgagttgttgggattccag
 base pairs
 accgagtgcggttagagggcgaggaccaccaagtctcgtaagaggacggagtcggagggctcaacaaccctaaggctc
 4276 to 4350

Eco88I
 BsoBI

70/173

NspI
 PaeI Mph1103I
 Ppu10I EcoT22I
 gcattgcattgaccaggctcagctaattttgtttttgttagagacgggtttcaccataattggccaggctggtc
 base pairs
 cgtaactggtccgagtcgattaaaaaaaccatctctgccccaaaagtgtataaccgggtccgaccag
 4351 to 4425
 BbuI Zsp2I CelII
 SphI Bsp1720I
 NsiI Bpu1102I
 BsmBI
 CfrI
 BalI
 MscI
 MluNI
 EaeI

FIG. 12-30

71/173

BsaI Eco130I
 StyI
 EcoT14I BstXI
tccaaactcctaattctcaggatctaccacaccttggcctcccaaatgctgggattacaggcgtgaaccactgct
base pairs
aggttgaggattagagtcactagatgggtggaaccggagggtttaacgacccctaattgtccgcacttggtgacga
4426 to 4500
Eco31I BssT1I
 ErhI

FIG. 12-31

BbiII NcoI
 HinII StyI
 AclI AatII EcoT14I
 DraI
 cccttcctgtccttctgtattttaaataactataaccagcaggagcgtccagacacagcataggctacctgcc
 base pairs
 gggaaggacaggaactaaaattttattgataggtcgtcctcctgcaggctctgtgtcgtatccgatggacgg
 4501 to 4575
 Msp17I BstII
 BsaHI ErhI
 Hsp92I BspMI
 72/173

Eco130I BsrFI PflMI
 DsaI AgeI Bse118I
 BsaWI AccB7I
 atggcccaaccgggtggacatttgagttgcttggtggcactgtcctctcatgctgggtccactcagtagatg
 base pairs
 taccgggttgccaccctgttaactcaacgaaccgtgacaggagtagtaccgaaccaggtagtcatctac
 4576 to 4650
 BssAI Esp1396I
 BstDSI PinaI Van91I
 Bsp19I Cfr10I

FIG. 12-32

EaeI AlwNI
 cctgttgaattgggtacgcggccagcttctgttggaatgtgtgcagttaggggtgtggaaagtccccagggtctcccc
 base pairs
 ggacaacttaaccatgcgcgcggtcgaagacacaccttacacacagtcfaatccacacctttcaggggtccgaggggg
 4651 to 4725
 CfrI

73/173

NspI
 PaeI Mph1103I
 Ppu10I EcoT22I SexAI
 agcaggcagaagtatgcaaaagcatgtcatctcaattagtcagcaaccagggtgtggaaaaagtcctccagggtccccag
 base pairs
 tcgtccgtcttcatacgtttcgtacgttagagttaatcagtcgttggtccacaccttttcagggggtccgagggggtc
 4726 to 4800
 BbuI Zsp2I
 SphI
 NsiI

FIG. 12-33

74/173

NspI
PaeI Mph1103I
Ppu10I EcoT22I
caggcagaagtatgcaaagcatgcatctcaattagtcagcaaccatagtcgcgcccctaactccgcccattcccgc
base pairs
gtccgtcttcatacgtttcgtacgtagagtgtaatacagtcgttggtatcagggcggggattgaggcgggtagggcg
4801 to 4875

BbuI Zsp2I
SphI
NsiI

NcoI Bsp19I
StyI BstDSI
EcoT14I
ccctaactccgcccagttccgcccattctccgcccattggctgactaatTTTTTTTatttatgtagagccgagg
base pairs
gggattgagcgcggtcaaggcgggtaagagcggggtaccgactgattaaaaaaaaataacgtctccggctcc
4876 to 4950

BstT1I
ErhI Eco130I
DsaI

FIG. 12-34

SseBI AvrII
 Eco147I BlnI
 StuI BstXI
 BglI BseRI
 ccgcctcggcctctgagctattccagaagtagtgaggaggctttttggaggcctaggcttttgcaaaaagctc c
 base pairs
 ggaggagccggagactcgataaaggcttctcatcactcctccgaaaaaacctccggatccgaaaacggtttttcgagg
 4951 to 5025
 SfiI
 AatI StyI
 Pme55I ErhI
 EcoT14I Eco130I

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Ama87I
 Eco88I BseRI
 AvaI BsoBI
 SfiI Apol
 tcgaggaactgaaaaaccagaaagttaattccctatatagtgagtcgtattaaattcgtaatcatggtcatagctgt
 base pairs
 agctccttgacttttggcttttcaattaaggatatactcagcataatttaagcatttagtaccagtagtcgaca
 5026 to 5100
 XhoI BcoI
 Sfr274I
 PaeR7I
 BstSFI
 Acsi

FIG. 12-35

76/173

AccBSI
BsrBI
ttcctgtgtgaaattgttatccgctcacaaattccacacaacatacagagccggaagcataaagtgtaaagcctggg
base pairs
aaggacacactttaacaataggcgagtggttaagggtgtgtgtatgctcggccttcgtatttcacatttcggaccc
5101 to 5175
BstD102I

AccB1I
BshNI
gtgcctaagtgtgagctaaactcacattaatgctgtgctcactgcccgcttccagtcgggaaacctgtcgt
base pairs
cacggattactcactcgattgagtgtaattaacgcaacgcgagtgacgggcgaaaggtcagccctttggacagca
5176 to 5250
Bani
Eco64I
VspI
PshBI
AsnI
AseI

FIG. 12-36

VspI
 MspA1I
 PvuII PshBI EaeI
 gccaagtgcattaatgaatcgcccaacgcggggagagcggttgcgtattgggcgctcttccgcttcctcgc
 base pairs
 cggtcgacgtaattacttagccggttgcgccctctcgcgaacgcataaacccgcgagaaggcgaaggagcg
 5251 to 5325
 NspBII CfrI
 HaeII EarI
 Sapi
 Ksp632I
 77/173
 BstMCI
 BsaOI
 AccBSI
 BsrBI
 tcaactgactcgctcggtcggttcggtcggcgagcggtatcagctcactcaaaggcggtataacggttat
 base pairs
 agtgactgagcgacgcgagccagcaagccgacgcgctcgccatagtcgagtgagtttccgccattatgccaat
 5326 to 5400
 Bsh1285I
 BsiEI
 BstD102I
 Eam1104I
 BstH2I
 Bsp143II

FIG. 12-37

78/173

NspI

BspLU11I

ccacagaatcaggggataaacgcaggaagaacatgtgagcaaaaggccagcaaaaggccaggaaccgtaaaaaagg
base pairs
ggtgtcttagtccccctattgcgtcctttcttgtaactcgttttccggtcgttttccggtccttggcatttttcc
5401 to 5475

AflIII

DrdI

ccgcgttgctggcgtttttccataggctccgccccctgacgagcatcacaaaaatcgacgctcaagtcaagaggt
base pairs
ggcgcaacgacccgcaaaaaaggatccgaggcgggggactgctcgtagtggttttagctgcgagttcagtcctcca
5476 to 5550

FIG. 12-38

BsiI
 ggcgaaacccgacaggactataaagataccaggcggtttccccctggaagctccctcgtagcgtctcctgttccga
 base pairs
 ccgcttgggctgcctgatatttctatggtccgcaaaaggggaccttcgagggagcacgcgagaggaaggct
 5551 to 5625
 BssSI
 79/173
 BstH2I
 Bsp143II
 SfiI
 ccctgccgcttacccggatacctgtccgcctttctcccttcgggaagcgtggcgctttctcaatgctcacgctgta
 base pairs
 gggacggcggaatggcctatggacagggcggaagagggaagcccttcgcaccgcgaaagagttacgagtgcgacat
 5626 to 5700
 HaeII
 BstSFI

FIG. 12-39

BsiHKAI	NspBII	80/173
Alw44I	BstMCI	
VneI Bbv12I	BsaOI	

ggtatctcagttcgggtgtaggtcggtcccaagctgggctgtgtgcacgaaccccccggttcagccccgaccgct
 base pairs
 ccataaggtcaagccacatccagcaagcgaggttcgacccgacacacgtgcttgggggcaagtcgggctggcgga
 5701 to 5775

ApalI	Bsh1285I
AspHI	BsiEI
Alw21I	MspAII

BsaWI	AlwNI
-------	-------

gagccttatccggtaactatcggtcttgagtcacacccggtgaagacacgacttatcgccactggcagcagccactg
 base pairs
 cgcggaataggccattgatagcagaactcaggttgggccattctgtgctgaatagcggtgaccgtcggtcggtgac
 5776 to 5850

FIG. 12-40

81/173

SfclI

gtaacaggattagcagagcgaggatgtaggcgggtgctacagaggtcttgaagtggcctaactacgggtaca
base pairs
cattgtccctaatacgtctcgctccatacatccgccacgatgtctcaagaacttcaccacggattgatgccgatgt
5851 to 5925

BstSFI

Eco57I

ctagaagaacagtatttgggtatctgcgctctgctgaagccaggttaccttcggaaaaagagtggtagctcttgat
base pairs
gatcttcttgatcataaaaccatagacgcgagacgacttcggtcaatggagcccttttctcaaccatcgagaacta
5926 to 6000

FIG. 12-41

MflI
 XhoII
 NspBII
 BstYI
 BstX2I
 MspAII
 6001 to 6075

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MflI
XhoII

ctcaagaagatcctttgatcttttctacgggtctgacgctcagtggaacgaaactcacgttaagggattttgg
base pairs
gagttcttctaggaactagaaaagatgccccagactgcgagtcaccttgcttttgagtgcgaattccctaaaacc
6076 to 6150

BstYI
BstX2I

FIG. 12-42

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RcaI	MflI	MflI	DraI
	XhoII	XhoII	
tcataagattatcaaaaaggatccttcacctagatccttttaaatataaaatgaagtttttaaatcaatctaaagta			
base pairs			
agtactctaatagtttttcctagaagtggtggtcctaggaataatttaattttacttcaaaatttagttagatttcacat			
6151 to 6225			
BspHI	BstYI	BstYI	
	BstX2I	BstX2I	

tatatgagtaaaacttggtctgacagttaccaatgcttaatcagtgaggcacctatctcagcgatctgtctatttc	AccB1I
base pairs	BshNI
atatactcatttgaaccagactgtcaatgggttacgaattagtcactccgtggatagatcgctagacagataaag	
6226 to 6300	
	BanI
	Eco64I

FIG. 12-43

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Eam1105I

AspEI

gttcacccatagttgcctgactccccgctcgtgtagataactacgatacgggagggttaccatctggccccagtg
base pairs

caagtaggtatcaacggactgaggggcagcacatctattgatgctatgccctcccgaatggtagaccgggtcac
6301 to 6375

EclHKI

AhdI

Cfr10I

BsrDI

BsaI

BssAI

BpmI

BglI

ctgcaatgataccgcgagaccacgctcaccggctccagatttatcagcaataaaccagccagccggaaggccg
base pairs

gacgttactatggcgctctgggtgcgagtggccgaggtctaaatagtcgttatttggtcggtcggccttccccggc
6376 to 6450

Eco31I

BsrFI

GsuI

Bse118I

FIG. 12-44

VspI
PshBI
agcgagaagtggctcctgcaactttatccgcctccatccagtcctattattgttgccgggaagctagagtaagta
base pairs
tcgcgtcttcaccaggacgttgaatataggcggttaggtcagataattaacaacggcccttcgatctcatcat
6451 to 6525

AsnI
AseI

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AviII BstSFI MslI
FspI SfiI
gttcgccagttaatagtttgcgcaacgttggtgccattgctacaggcatcgtggtgtcacgctcgtcgtttggta
base pairs
caagcgggtcaattatcaaacgcgttgcaacaacggtaacgatgtccgtagcaccacagtgcgagcagcaaacat
6526 to 6600

Acc16I BsrDI
Psp1406I

FIG. 12-45

BsaWI
 tggcttcattcagctccggttcccaacgataaggcgaggttacatgatcccccatgttgtcaaaaaagcgggta
 base pairs
 accgaagtaagtcgaggccaagggttgctagtccgctcaatgtactaggggtacaacacggttttttcgccaat
 6601 to 6675

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BstMCI
 PvuI BsiEI
 BsaOI EaeI MslI
 gctccttcggtcctccgatcgttgtcagaagtaagttggccgcagtggtatcactcatgggtatggcagcactgc
 base pairs
 cgaggaagccaggaggtagcaacagtccttcattcaaccggcggtcacaatagtgtgagtaaccaataccgtcgtgacg
 6676 to 6750

BspCI CfrI
 Bsh1285I
 Ple19I

FIG. 12-46

Acc113I
 Eco255I
 ataattcttactgtcatgccatccgtaagatgcttttctgtgactgggtgactcaaccaagtcattctgag
 base pairs
 tattaagagaatgacagtagcgtaggcattctacgaaaagacactgaccactcatgagttgggttcagtaagactc
 6751 to 6825
 ScaI

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BbiII
 BstMCI
 BsaOI
 BcgI
 BsiII
 BsiEI
 Bsp17I
 BsaHI
 Hsp92I
 aatagtgtatgcggcgaccgagttgctcttgcggcggtcaataacgggataataccgcccacatagcagaactt
 base pairs
 ttatcacatacgccgctggctcaacgagaacgggcccgcagttatgccctattatggcgcggtgtatcgtcttgaa
 6826 to 6900

FIG. 12-47

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Alw21I	XmnI	MflI	MflI
DraI	Psp1406I	XhoII	NspBII XhoII

taaaagtgcctcatcattggaaaacgttcttcggggcgaaaactctcaaggatcttaccgctgttgagatccagtt
 base pairs
 attttcacgagtagtaaccttttgcaagaagccccgcttttgagagttcctagaatggcgacaactctaggtcaa
 6901 to 6975

BsiHKAI	Asp700I	BstYI	MspAII BstYI
Bbv12I		BstX2I	BstX2I

BssSI	Eco57I
Alw44I Bbv12I	
VneI BsiHKAI	

cgatgtaaccactcgtgcacccaactgatcttcagcatcttttactttcaccagcgtttctgggtgagcaaaa
 base pairs
 gctacattgggtgagcacgtgggtgactagaagtcgtagaaaatgaaagtgggtcgcaagaccactcggtttt
 6976 to 7050

ApalI Alw21I
BsiI
AspHI

FIG. 12-48

MsII
 EarI
 Ham1104I
 caggaaggcaaaatgccgcaaaaaagggaataaggcgacacggaaatggtgaatactcatactcttccttttc
 base pairs
 gtccttcggttttacggcggtttttcccttattcccgctgtgcctttacaacttatgagtatgagaaggaaaaag
 7051 to 7125
 Ksp632I

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SspI
 RcaI
 AccBSI
 BsrBI
 aatattattgaagcatttatcagggtattgtctcatgagcggatacatatttgaatgtatttagaaaaataaac
 base pairs
 ttataaacttcgtaaatagtcaccaataacagagtagtgcctatgtataaaacttacataaatctttttatttg
 7126 to 7200
 BspHI
 BstD102I

FIG. 12-49

SfCI
 aaataggggttcgcgcacatttccccgaaaagtgcacacctgacgcgccctgtagggcgcatatagcgcggcgg
 base pairs
 ttatatccccaaggcgcgtgtaaaaggggcttttcacgggtggactgcgcgggacatcgccgcgtaattcgcgcgcgc
 7201 to 7275

BstSFI

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AccBSI
 BstH2I HaeII BstD102I
 Bsp143II BsrBI
 gtgtggtggttacgcgcagcgtgaccgctacacttgccagcgccttagcgcgccctccttctcgctttcttccctt
 base pairs
 cacaccaccaatgcgcgtcgactggcgatgtgaacggtcgcgggatcgcgggcgaggaagcgaagaaagggaa
 7276 to 7350

HaeII Bsp143II
 BstH2I

FIG. 12-50

91/173

BsrFI
BssAI NaeI
MroNI Bse118I
cctttctgccacgttcgccggctttcccggtcaagctctaaatcggggcatccctttagggtccgatttagtg
base pairs
ggaaagagcgggtgcaagcggccgaaaggggcagttcgagatttagccccgtaggggaaatcccaaggctaatacac
7351 to 7425
NgoAIV
NgoMI
Cfr10I
AccB1I
BshNI
BsaAI
base pairs
ctttacggcacctcgacccccaaaaacttgattagggatggttcacgtagtgggccatcgccctgatagacgg
base pairs
gaaatgccgtggagctgggggtttttgaactaatcccactaccacgaagtgcacccggtagcgggactatctgcc
7426 to 7500
BaNi
Eco64I
DraIII

FIG. 12-51

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DrdI

ttttcgcccttgacgttgaggtccacgttctttaatagtggaactctgttccaaactgggaacaacactcaacc
base pairs
aaaaagcgggaaactgcaacctcaggtgcaagaaattatcacctgagaacaaggttgaccttggtgagttgg
7501 to 7575

ctatctcgggtctattctttgatattataagggattttgcccgaatttcggcctattgggttaaaaatgagctgattt
base pairs
gatagagccagataagaaaaactaaatattccctaaaacggctaagccggataaccaattttttactcgactaaa
7576 to 7650

FIG. 12-52

ApoI ApoI SspI Psp1406I
 aacaaaaatttaacgcgaattttaacaaaaataataacggtttacaattt base pairs
 ttgtttttaaatgcttaaaattgttttataatttgcaaatgttataa 7651 to 7699
 ACSI ACSI

Table by Enzyme Name

Enzyme name	No. cuts of sites	Positions	Recognition sequence	
AatI	3	3446 3546 5002	agg/cct	<u>More info</u>
AatII	5	451 504 587 773 4550	gacgt/c	<u>More info</u>
Acc113I	1	6804	agt/act	<u>More info</u>
Acc16I	2	21 6546	tgc/gca	<u>More info</u>
Acc65I	3	2264 3434 3998	g/ gtacc	<u>More info</u>
AccB1I	8	791 2264 3065 3434 3998 5175 6272 7432	g/ gyrcc	<u>More info</u>
AccB7I	6	1445 1482 1775 1796 2644 4587	ccannnn/ntgg	<u>More info</u>
AccBSI	4	5126 5367 7168 7332	gagcgg	<u>More info</u>
Ac1NI	1	326	a/ ctagt	<u>More info</u>
AcSI	8	912 1990 2244 2994 3963 5075 7656 7667	r/ aatty	<u>More info</u>
AcYI	6	448 501 584 770 4547 6861	gr/cgyc	<u>More info</u>

FIG. 12-53

AflIII	3	2702 3796 5431	a/ crygt	<u>More info</u>
AgeI	1	4584	a/ ccggt	<u>More info</u>
AhdI	2	4150 6324	gacnnn/nngtc	<u>More info</u>
Alw21I	6	894 1576 2330 5749 6910 6995	gwgw/c	<u>More info</u>
Alw44I	2	5745 6991	g/ tgcac	<u>More info</u>
AlwNI	6	1147 1273 1775 3091 4678 5847	cagnnn/ctg	<u>More info</u>
Ama87I	3	4034 4330 5025	c/ ycgrg	<u>More info</u>
AocI	3	1034 1046 3256	cc/ tnagg	<u>More info</u>
ApaI	1	4202	gggcc/c	<u>More info</u>
ApalI	2	5745 6991	g/ tgcac	<u>More info</u>
ApoI	8	912 1990 2244 2994 3963 5075 7656 7667	r/ aatty	<u>More info</u>
AseI	4	334 5202 5261 6496	at/ taat	<u>More info</u>
AsnI	4	334 5202 5261 6496	at/ taat	<u>More info</u>
Asp700I	5	1107 2481 3506 3906 6923	gaann/nnttc	<u>More info</u>
Asp718I	3	2264 3434 3998	g/ gtacc	<u>More info</u>

FIG. 12-54

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AspEI	2	4150	6324						gacnnn/nngtc	More info
AspHI	6	894	1576	2330	5749	6910	6995		gwgcw/c	More info
AspI	1	3674							gacn/nngtc	More info
AtsI	1	3674							gacn/nngtc	More info
AvaI	3	4034	4330	5025					c/ ycgrg	More info
AviII	2	21	6546						tgc/gca	More info
AvrII	2	3109	5003						c/ ctagg	More info
BalI	5	184	238	3300	3653	4414			tgg/ccaa	More info
BamHI	1	3992							g/ gatcc	More info
BanI	8	791	2264	3065	3434	3998	5175		g/ gyrcc	More info
		6272	7432							
BanII	5	894	1017	1623	3526	4202			grgcy/c	More info
BanIII	1	939							at/ cgat	More info
BbiII	6	448	501	584	770	4547	6861		gr/cgyc	More info
BbrPI	1	2705							cac/gtg	More info
BbsI	2	2512	4216						gaagac	More info
BbuI	4	2930	4355	4750	4823				gcatg/c	More info
Bbv12I	6	894	1576	2330	5749	6910	6995		gwgcw/c	More info
Bbv16II	2	2512	4216						gaagac	More info
BcgI	4	941	2556	4321	6851				cgannttttgc	More info

FIG. 12-55

BclI	1	969	t/ gatca	<u>More info</u>
BcoI	3	4034 4330 5025	c/ ycgrg	<u>More info</u>
BglI	5	14 417 538 4956 6444	gccnnnn/nggc	<u>More info</u>
BglII	2	932 3409	a/ gatct	<u>More info</u>
BlnI	2	3109 5003	c/ ctagg	<u>More info</u>
BlpI	3	1200 2337 4366	gc/tnagc	<u>More info</u>
BpiI	2	2512 4216	gaagac	<u>More info</u>
BpmI	10	1015 1279 1772 2781 2842 3022	ctggag	<u>More info</u>
		3892 4097 4259 6414		
Bpu1102I	3	1200 2337 4366	gc/tnagc	<u>More info</u>
Bpu14I	3	1603 1988 2423	tt/cgaa	<u>More info</u>
BpuAI	2	2512 4216	gaagac	<u>More info</u>
Bsa29I	1	939	at/ cgat	<u>More info</u>
BsaAI	3	666 2705 7473	yac/gtr	<u>More info</u>
BsaHI	6	448 501 584 770 4547 6861	gr/cgyc	<u>More info</u>
BsaI	3	3380 4427 6396	ggtctc	<u>More info</u>
BsaMI	3	1886 3631 3936	gaatgc	<u>More info</u>
BsaOI	7	42 424 928 5347 5771 6694 6843	cgry/cg	<u>More info</u>
BsaWI	6	3200 3995 4584 5637 5784 6615	w/ ccggw	<u>More info</u>
BscI	1	939	at/ cgat	<u>More info</u>

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FIG. 12-56

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Bse118I	3	4584	6404	7368	r/ ccggy	<u>More info</u>
Bse211I	3	1034	1046	3256	cc/ tnagg	<u>More info</u>
BseCI	1	939			at/ cgat	<u>More info</u>
BseRI	5	1337	1671	3725 4989 5027	gaggag	<u>More info</u>
BsgI	3	2315	3212	4264	gtgcag	<u>More info</u>
Bsh1285I	7	42	424	928 5347 5771 6694 6843	cgry/cg	<u>More info</u>
BshNI	8	791	2264	3065 3434 3998 5175	g/ gyrcc	<u>More info</u>
		6272	7432			
BsiEI	7	42	424	928 5347 5771 6694 6843	cgry/cg	<u>More info</u>
BsiHKAI	6	894	1576	2330 5749 6910 6995	gwgcw/c	<u>More info</u>
BsiI	2	5609	6993		ctcgtg	<u>More info</u>
BsmBI	3	2023	2773	4397	cgtctc	<u>More info</u>
BsmI	3	1886	3631	3936	gaatgc	<u>More info</u>
BsoBI	3	4034	4330	5025	c/ ycgrg	<u>More info</u>
Bsp106I	1	939			at/ cgat	<u>More info</u>
Bsp119I	3	1603	1988	2423	tt/cgaa	<u>More info</u>
Bsp120I	1	4198			g/ ggccc	<u>More info</u>
Bsp1407I	2	270	3471		t/ gtaca	<u>More info</u>
Bsp143II	5	2519	5309	5679 7318 7326	rgcgc/y	<u>More info</u>
Bsp1720I	3	1200	2337	4366	gc/tnagc	<u>More info</u>
Bsp19I	6	686	3324	3424 3600 4574 4910	c/ catgg	<u>More info</u>

FIG. 12-57

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BspCI	2	42 6694	cgat/cg	<u>More info</u>
BspDI	1	939	at/ cgat	<u>More info</u>
BspHI	3	1891 6151 7159	t/ catga	<u>More info</u>
BspLU11I	1	5431	a/ catgt	<u>More info</u>
BspMI	2	1913 4574	acctgc	<u>More info</u>
BspXI	1	939	at/ cgat	<u>More info</u>
BsrBI	4	5126 5367 7168 7332	gagcgg	<u>More info</u>
BsrDI	4	245 2827 6383 6565	gcaatg	<u>More info</u>
BsrFI	3	4584 6404 7368	r/ ccggy	<u>More info</u>
BsrGI	2	270 3471	t/ gtaca	<u>More info</u>
BssAI	3	4584 6404 7368	r/ ccggy	<u>More info</u>
BssSI	2	5609 6993	ctcgtg	<u>More info</u>
BssT1I	13	686 1950 2226 3109 3324 3424 3547 3600 4077 4456 4574 4910 5003	c/ cwwgg	<u>More info</u>
BstBI	3	1603 1988 2423	tt/cgaa	<u>More info</u>
BstD102I	4	5126 5367 7168 7332	gagcgg	<u>More info</u>
BstDSI	7	686 1062 3324 3424 3600 4574 4910	c/ crygg	<u>More info</u>
Bsth2I	5	2519 5309 5679 7318 7326	rgcgc/y	<u>More info</u>

FIG. 12-58

BstI	1	3992		g/ gatcc	<u>More info</u>
BstMCI	7	42 424 928 5347 5771 6694 6843		cgry/cg	<u>More info</u>
BstSFI	8	944 2144 4220 5058 5696 5887		c/ tryag	<u>More info</u>
		6565 7250			
BstSNI	1	666		tac/gta	<u>More info</u>
BstX2I	12	932 2400 2634 3409 3992 4030		r/ gatcy	<u>More info</u>
		6072 6083 6169 6181 6949 6966			
BstXI	3	3076 3325 4473		ccannnn/ntgg	<u>More info</u>
BstYI	12	932 2400 2634 3409 3992 4030		r/ gatcy	<u>More info</u>
		6072 6083 6169 6181 6949 6966			
BstZI	1	925		c/ ggccg	<u>More info</u>
Bsu15I	1	939		at/ cgat	<u>More info</u>
Bsu36I	3	1034 1046 3256		cc/ tnagg	<u>More info</u>
CciNI	1	925		gc/ggccgc	<u>More info</u>
CelII	3	1200 2337 4366		gc/tnagc	<u>More info</u>
Cfr10I	3	4584 6404 7368		r/ ccggy	<u>More info</u>
Cfr9I	1	4034		c/ ccggg	<u>More info</u>
CfrI	10	152 182 236 925 3298 3651 4412		y/ ggccr	<u>More info</u>
		4669 5270 6712			
ClaiI	1	939		at/ cgat	<u>More info</u>
Csp45I	3	1603 1988 2423		tt/cgaa	<u>More info</u>
CvnI	3	1034 1046 3256		cc/ tnagg	<u>More info</u>

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FIG. 12-59

DraI	5	3981	4523	6190	6209	6901	ttt/aaa	<u>More info</u>
DraII	3	3291	4198	4225			rg/gnccy	<u>More info</u>
DraIII	1	7476					cacnnn/gtg	<u>More info</u>
DrdI	3	1076	5539	7520			gacnnnn/nngtc	<u>More info</u>
DsaI	7	686	1062	3324	3424	3600 4574	c/ cry9g	<u>More info</u>
		4910						
EaeI	10	152	182	236	925	3298 3651 4412	y/ ggccr	<u>More info</u>
		4669	5270	6712				<u>More info</u>
EagI	1	925					c/ ggccg	<u>More info</u>
Eam1104I	5	58	2482	2793	5314	7118	ctcttc	<u>More info</u>
Eam1105I	2	4150	6324				gacnnn/nngtc	<u>More info</u>
EarI	5	58	2482	2793	5314	7118	ctcttc	<u>More info</u>
Ecl1136II	1	892					gag/ ctc	<u>More info</u>
EclHKI	2	4150	6324				gacnnn/nngtc	<u>More info</u>
EclXI	1	925					c/ ggccg	<u>More info</u>
Eco105I	1	666					tac/gta	<u>More info</u>
Eco130I	13	686	1950	2226	3109	3324 3424	c/ cwwgg	<u>More info</u>
		3547	3600	4077	4456	4574 4910		
		5003						
Eco147I	3	3446	3546	5002			agg/cct	<u>More info</u>

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FIG. 12-60

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Eco24I	5	894	1017	1623	3526	4202	grgcy/c	<u>More info</u>
Eco255I	1	6804					agt/act	<u>More info</u>
Eco31I	3	3380	4427	6396			ggtctc	<u>More info</u>
Eco32I	1	952					gat/atc	<u>More info</u>
Eco52I	1	925					c/ggccg	<u>More info</u>
Eco57I	7	1210	2446	2488	3271	3314 5963	ctgaag	<u>More info</u>
		7011						
Eco64I	8	791	2264	3065	3434	3998 5175	g/gyrcc	<u>More info</u>
		6272	7432					
Eco72I	1	2705					cac/gtg	<u>More info</u>
Eco81I	3	1034	1046	3256			cc/tnagg	<u>More info</u>
Eco88I	3	4034	4330	5025			c/ycgrg	<u>More info</u>
EcoICRI	1	892					gag/ctc	<u>More info</u>
EcoNI	4	1259	1338	1684	3723		cctnn/nnnagg	<u>More info</u>
EcoO109I	3	3291	4198	4225			rg/gnccy	<u>More info</u>
EcoRI	3	912	1990	2994			g/aattc	<u>More info</u>
EcoRV	1	952					gat/atc	<u>More info</u>
EcoT14I	13	686	1950	2226	3109	3324 3424	c/cwwgg	<u>More info</u>
		3547	3600	4077	4456	4574 4910		
		5003						
EcoT22I	5	3703	3850	4357	4752	4825	atgca/t	<u>More info</u>

FIG. 12-61

ErhI	13	686	1950	2226	3109	3324	3424	c/ cwwgg	<u>More info</u>
		3547	3600	4077	4456	4574	4910		
		5003							
Esp1396I	6	1445	1482	1775	1796	2644	4587	ccannnn/ntgg	<u>More info</u>
Esp3I	3	2023	2773	4397				cgtctc	<u>More info</u>
FauNDI	1	560						ca/ tatg	<u>More info</u>
FbaI	1	969						t/ gatca	<u>More info</u>
FriOI	5	894	1017	1623	3526	4202		grgcy/c	<u>More info</u>
FspI	2	21	6546					tgc/gca	<u>More info</u>
GsuI	10	1015	1279	1772	2781	2842	3022	ctggag	<u>More info</u>
		3892	4097	4259	6414				
HaeII	5	2519	5309	5679	7318	7326		rgcgc/y	<u>More info</u>
HinII	6	448	501	584	770	4547	6861	gr/cgyc	<u>More info</u>
HincII	3	311	446	842				gty/rac	<u>More info</u>
HindII	3	311	446	842				gty/rac	<u>More info</u>
HindIII	3	918	1394	2183				a/ agctt	<u>More info</u>
Hsp92I	6	448	501	584	770	4547	6861	gr/cgyc	<u>More info</u>
KpnI	3	2268	3438	4002				ggtac/c	<u>More info</u>
Ksp22I	1	969						t/ gatca	<u>More info</u>
Ksp632I	5	58	2482	2793	5314	7118		ctcttc	<u>More info</u>
LspI	3	1603	1988	2423				tt/cgaa	<u>More info</u>
MfeI	2	1091	3773					c/ aattg	<u>More info</u>
MflI	12	932	2400	2634	3409	3992	4030	r/gatcy	<u>More info</u>

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FIG. 12-62

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MLuNI	5	6072 6083 6169 6181 6949 6966	tgg/cca	<u>More info</u>
Mph1103I	5	184 238 3300 3653 4414	atgca/t	<u>More info</u>
MroNI	1	3703 3850 4357 4752 4825	g/ ccggc	<u>More info</u>
MscI	5	7368	tgg/cca	<u>More info</u>
MslI	10	184 238 3300 3653 4414	caynn/nnrtg	<u>More info</u>
		691 2094 2703 3323 3489 4047		
		4094 6576 6735 7094		
Msp17I	6	448 501 584 770 4547 6861	gr/cgyc	<u>More info</u>
MspA1I	7	71 2341 2731 5255 5773 6018 6959	cmg/ckg	<u>More info</u>
MunI	2	1091 3773	c/ aattg	<u>More info</u>
Mva1269I	3	1886 3631 3936	gaatgc	<u>More info</u>
NaeI	1	7370	gcc/ggc	<u>More info</u>
NcoI	6	686 3324 3424 3600 4574 4910	c/ catgg	<u>More info</u>
NdeI	1	560	ca/ tatg	<u>More info</u>
NgoAIV	1	7368	g/ ccggc	<u>More info</u>
NgomI	1	7368	g/ ccggc	<u>More info</u>
NotI	1	925	gc/ggccgc	<u>More info</u>
NsiI	5	3703 3850 4357 4752 4825	atgca/t	<u>More info</u>
NspBII	7	71 2341 2731 5255 5773 6018 6959	cmg/ckg	<u>More info</u>
Nspi	5	2930 4355 4750 4823 5435	rcatg/y	<u>More info</u>
NspV	3	1603 1988 2423	tt/cgaa	<u>More info</u>
PaeI	4	2930 4355 4750 4823	gcatg/c	<u>More info</u>
Paer7I	1	5025	c/ tcgag	<u>More info</u>

FIG. 12-63

	6	1445	1482	1775	1796	2644	4587		ccannnn/ntgg	More info
PfIMI									a/ ccggt	More info
PinAI	1	4584							cgat/cg	More info
Ple19I	2	42 6694							cac/gtg	More info
PmaCI	1	2705							agg/cct	More info
Pme55I	3	3446 3546 5002							cac/gtg	More info
PmlI	1	2705							a/ tgcat	More info
Ppu10I	5	3699 3846 4353 4748 4821							at/ taat	More info
PshBI	4	334 5202 5261 6496							gagct/c	More info
Psp124BI	1	894							aa/cggt	More info
Psp1406I	3	6550 6923 7687							c/ccggg	More info
PspAI	1	4034							ccc/ggg	More info
PspALI	1	4036							g/gggcc	More info
PspOMI	1	4198							ctgca/g	More info
PstI	2	948 2148							cgat/cg	More info
PvuI	2	42 6694							cag/ctg	More info
PvuII	3	71 2341 5255							t/ catga	More info
RcaI	3	1891 6151 7159							gagct/c	More info
SacI	1	894							gctcttc	More info
SapI	2	2483 5314							agt/act	More info
ScaI	1	6804							a/ ccwgggt	More info
SexAI	1	4769							c/ tryag	More info
SfiI	8	944 2144 4220 5058 5696 5887								

FIG. 12-64

SfiI	1	6565	7250	ggccnnnn/nggcc	<u>More info</u>
Sfr274I	1	4956		c/ tgcag	<u>More info</u>
SfuI	3	5025		tt/cgaa	<u>More info</u>
SmaI	1	1603	1988 2423	ccc/ggg	<u>More info</u>
SnaBI	1	4036		tac/gta	<u>More info</u>
SpeI	1	666		a/ ctagt	<u>More info</u>
SphI	4	326		gcatg/c	<u>More info</u>
SseBI	3	2930	4355 4750 4823	agg/cct	<u>More info</u>
SspBI	2	3446	3546 5002	t/ gtaca	<u>More info</u>
SSPI	6	270	3471	aat/att	<u>More info</u>
SstI	1	179	226 3571 4164 7128 7681	gagct/c	<u>More info</u>
StuI	3	894		agg/cct	<u>More info</u>
StyI	13	3446	3546 5002	c/ cwwgg	<u>More info</u>
		686	1950 2226 3109 3324 3424		
		3547	3600 4077 4456 4574 4910		
		5003			
Tth111I	1	3674		gacn/nngtc	<u>More info</u>
Van91I	6	1445	1482 1775 1796 2644 4587	ccannnn/ntgg	<u>More info</u>
VneI	2	5745	6991	g/ tgcac	<u>More info</u>
VspI	4	334	5202 5261 6496	at/ taat	<u>More info</u>
XbaI	1	3811		t/ ctaga	<u>More info</u>
XcmI	2	1948	2897	ccannnnn/nnntgg	<u>More info</u>

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FIG. 12-65

XhoI	1	5025			c/ tcgag	<u>More info</u>
XhoII	12	932 2400 2634 3409 3992 4030			r/ gatcy	<u>More info</u>
		6072 6083 6169 6181 6949 6966				
XmaI	1	4034			c/ ccggg	<u>More info</u>
XmaIII	1	925			c/ ggccg	<u>More info</u>
XmnI	5	1107 2481 3506 3906 6923			gaann/nnttc	<u>More info</u>
Zsp2I	5	3703 3850 4357 4752 4825			atgca/t	<u>More info</u>

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The following endonucleases were selected but don't cut this sequence:

AccI, AccIII, AfeI, AflII, Aor51HI, AscI, BbeI, BfrI, BsaBI, Bse8I, BseAI, BsePI, Bsh1365I, BsiMI, BsiWI, Bsp13I, Bsp68I, BspEI, BspTI, BsrBRI, BssHII, Bst1107I, Bst98I, BstEII, BstPI, Cfr42I, CpoI, CspI, Eco47III, Eco91I, EcoO65I, EheI, FseI, HpaI, Kasi, Kpn2I, KspI, MamI, MluI, MroI, MspCI, NarI, NheI, NruI, PacI, Pfl23II, PmeI, PpuMI, PshAI, Psp5II, PspEI, PspLI, PstNHI, RsrII, SacII, SalI, SbfI, Sfr303I, Sgfi, SgrAI, SmiI, Sphi, SrfI, Sse8387I, SstII, SunI, SwaI, Vha464I

FIG. 12-66

FIG. 13A
FIG. 13B
FIG. 13C
FIG. 13D
FIG. 13E

cccatcgccattcaggctgcgcaactgttgggaaggcgatcgggtcgggcctcttcgctattacgccagctggcgaaaggcg
ggatgtgctgcaaggcgattaagttgggtaacgcccagggtttccagtcacgacgttgtaaaacgacggccagtgccaagct
gatctaataatcgaatggccattagcccatattattcattggttatatagcataaaatcaatattggctattggccattgcatacgttgatcca
tatcataatatgtacatttatattggctcatgtccaacattaccgccatgttgacattgatttagactagttattaatagtaatcaattacg
gggtcattagtticatagcccatatatggagttccgcgttacataacttacggtaaatggccgcctggcgaccgccagcgaccc
ccgcccgttgacgtcaatagtgacgtatgttcccatagtaacccaataggggactttccattgacgtcaatgggtggagtatttacg
gtaaactgccacttggcagtagcacatcaagtgtagtataatgccaaagtcgccccctattgacgtcaatgacggtaaatggccccgcct
agcattatgccagtagacatgaccttacggggagtttctacttggcagtagacatctacgtattagtcacgtctattaccatgggtatgcg
gtttggcagtagcaccaatggcggtggatagcgggttgactcacggggatttccaaagtcctccacccattgacgtcaatggggaggtt
tgtttggcaccacaaatcaacgggactttccaaaatgtcgtataacccccggccgttgacgcaaatggcggtagcggtgtacg
gtgggagggtctatataagcagagctcgttagtgaaccgtcagaattcaagcttgcggccgcagatctatcgatctgcagagatatac
(EcoRV)
acc

FIG. 13

FIG. 13A

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ATGCACAGTATGATCAGCTCAGTGGATGTGAAGTCAGAAGTTCCTGTGGCCTGGAGCCCATCTCACCTTTA
GACCTAAGGACAGACCTCAGGATGATGATGCCCGTGGTGACCCCTGTGTCCGTGAGAAAGCAATTGCAGCAG
GAATTACTTCTTATCCAGCAGCAGCAACAATCCAGAAGCAGCTTCTGTATAGCAGAGTTTCAGAAACAGCAT
GAGAACTTGACACGCGAGCACCCAGGCTCAGCTCAGGAGCATATCAAGGAACCTTCTAGCCATAAAACAGCAA
CAAGAACTCTAGAAAAGGAGCAGAAACTGGAGCAGCAGAGGCAAGAACAGGAAGTAGAGAGGCATCGCAGA
GAAACAGCAGCTTCCCTCTCAGAGGCAAAAGATAGAGGACGAGAAAGGCGCAGTGGCAAGTACAGAAGTAAAG
CAGAAGCTTCAAGAGTTCCTACTAGTAAATCAGCAACGAAAGACACTCCAACCTAATGGAAAATCATTCC
GTGAGCCGCATCCCAAGCTCTGGTACACGGCTGCCACACACATCATTTGGATCAAAGCTCTCCACCCCTT
AGTGGAAACATCTCCATCCCTACAAGTACACATTAACAGGAGCACAAAGATGCAAAGGATGATTTCCCCCTTCGA
AAAACCTGCCCTCTGAGCCCAACTTGAAGTGCGGTCCAGGTTAAACACAGAAAGTGGCAGAGAGAGAAAGCAGC
CCCTTACTCAGGCGGAAGGATGGAAATGTTGTCACTTCAATTCAGAAGAGCGAATGTTTGAGGTGACAGAAATCC
TCAGTCAGTAGCAGTTCTCCAGGCTCTGGTCCAGTTCACCAAACAATGGCCCACTGGAAAGTGTACTGAA
AATGAGACTTCGGTTTIGCCCCCTACCCCTCATGCGGAGCAAAATGGTTTCACAGCAACGCAATCTAAATTCAT
GAAGATTCCATGAACCTGCTAAGTCTTTATACCTCTCTCTTTTGCCCCAACATTACCTTGGGGCTTCCCCGCA
GTGCCATCCAGCTCAATGCTTCGAATTCACCTCAAAGAAAAGCAGAGTGTGAGACGCAGACGCTTAGGCAA
GGTGTTCCTCTGCTGGCAGTATGGAGGCAGCATCCCGGCATCTCCAGCCACCCCTCATGTACTTTAGAG
GGAAAGCCACCCAACAGCAGCCACAGGCTCTCCTGCAGCATTTATTTAATGAAAGAACAAATGCCACAGCAA
AAGCTTCTTGTAGCTGGTGGAGTTCCCTTACATCCTCAGTCTCCCTTGGCAACAAAAGAGAGAAATTTACCT
GGCATTAGAGTACCCACAAATTGCCCCGTACAGACCCCTGAACCGAACCCAGTCTGCACCTTTGCCCTCAG
AGCACGTTGGCTCAGCTGGTCAATTCACAGCAACACAGCAATTCCTTGGAGAAAGCAGAAATACACAGCAG
CAGATCCACATGAACAAACTGCTTTCGAAATCTATTGAACAACCTGAAGCAACCCAGGCAGTCACCTTGAGGAA
GCAGAGGAAGAGCTTCAGGGGACCCAGGCGATGCAGGAAGACAGAGCGCCCTCTAGTGGCAACAGCACTAGG
AGCGACAGCAGTGCTTGTGTGGATGACACACTGGGACAAGTTGGGGCTGTGAAGGTCAAGGAGGAACCCAGTG
GACAGTGATGAAGATGCTCAGATCCAGGAAATGGAATCTGGGAGCAGGCTGCTTTTATGCAACAGCCCTTC

FIG. 13B

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CTGGAACCCACGCACACAGTGGCTCTCTGTGCGCCCAAGCTCCGCTGGCTGCGGTTGGCATGGATGGATTAGAGAAACACCGTCTCGTCTCCAGGACTCACTCTTCCCCTGCTGCCCTCTGTGTTTACCTCACCCAGCAATGGACGCCCCCTCCAGCCTGGCTCTGCAACTGGAATTGCCCTATGACCCCTTGATGCTGAAACACACAGTGCCTTTGTGGCAATTCCACACCCACCCCTGAGCATGCTGGACGAAATACAGAGTATCTGGTCAAGCTGCAAGAACTGGGCTGCTAAATAAATGTGAGCGAATTCAAGGTCGAAAAGCCAGCCTGGAGGAAATACAGCTTGTTCATTCTGAAATCATCACTCACTGTTGTATGGCACCAACCCCTGGACGGACAGAAAGCTGGACCCAGGATACTCCTAGGTGATGACTCTCAAAAGTTTTTTTCCCTCATTAACCTTGTGGTGGACTTGGGGTGGACAGTGACACCACTTTGGAAATGAGCTACACTCGTCCGGTGTGCACGCATGGCTGTTGGCTGTGTCTCATCGAGCTGGCTTCCAAAGTGGCCTCAGGAGAGCTGAAGAAATGGGTTTGTGTGAGGCCCCCTGGCCATCACGCTGAAGAAATCCACAGCCATGGGGTTC TGCTTTTAAATTCAGTTGCAATTACCGCCAAATACTTGAGAGACCAACTAAATATAAGCAAGATATTGATTGTAGATCTGGATGTTACCATGGAAACCGTACCCAGCAGGCCCTTTTATGCTGACCCAGCATCCTGTACATT TCACTCCATCGCTATGATGAAGGAACTTTTCCCTGGCAGTGGAGCCCCCAATGAGGTTTCGGTTTATTCTCTTAGAGCCCCACCTTTTATTGTATCTTTTTCAGGTAATTGCATTGCA

FIG. 13C

[illegible]

ttttgtttgcaagcagcagattaccgcgcaaaaaaaaggatctcaaggagatccttttgatctttttctacgggggtctgacgctcagctg
gaacgaaaaactcacgttaagggatttttgctcatgagattatcaaaaaaggatcttcaccctagatcccttttaaatataaaatgaagtttta
aatcaatcaaaagtatatatgagtaaaacttggtctgacagttacccaatgcttaatacgtgagggcacctatctcagcgtatctgtctatttc
gttcatccatagtgtgcctgactccccgtcgtgtgtagataactacgatacgggagggctttaaccatctggccccagtgctcagcaatgata
ccccgagacccacggctcaccggctccagattatcagcaataaaaccagccaggaaaggccccgagggcgcagagagtggtcct
gcaactttatccgctccatccagctctatttaattgttgcgggaaagctagagtaagtgttcgccagtttaatagttttgccaacggtgtg
tgccattgctacaggcatcgtgggtgtcacgctcgtcgtttgtgtatggcttccattcagctccgggttccccaaagatcaaggcgaggttac
atgatacccccatgtttgcaaaaaagggttagtcccttcggctctccgatacgttgtcagaaagtaagtggccccgacgtgttatacact
catggttatggcagcactgcataattctctactgcatgccatccgtaagatgcttttctgtgactgggtgagttactcaaccaaagtcatt
ctgagaatagtgtatgcggcgaccgagttgctcttggccggcgctcaatacgggataataccggccacacatagcagaactttaaaaa
gtgctcatcattggaaaaagttcttcggggcgaaaaactctcaaggatcttaccgctgtgtgagatccagttcgatgtaacccacacgcgt
gcacccaactgatcttcagcatcttttaccacagcgtttctgggtgagcaaaaaacaggaaggcgaatgccgcaaaaaaagg
gaataaggcgcgacacggaaatgttgaatactcatactctctcttttcaatatattgaaagcatttatcagggttattgtctcatgagcg
gatacatatttgaatgtatttagaaaaataaacaataagggttcgcgcacatttccccgaaaaagtgccacctgacggcgccccgt
agcggcgcatlaagcgcggcggtgtgtgtgttacggcgagcgtgacccgtacacctggccagcgccctagcggccccgctccttt
cgcttctccctctcttcgcacgcttcggcgcttccccgtcaagctctaaatcggggcatcccttttaggggttccgatttagtgc
ttttacggcacctcgacccccaaaaaacttgatttaggggtgtatggtttcacgttagtggccatcgccctgatagacgggttttgcgccctt
gacgttgagtcacggtctttaatagtggactcttgttccaaactgggaacaacactcaaacctatctcgctctattcttttgatttataa
gggattttgcgatttcggcctattgggttaaaaaaatgagctgatttaacaaaaatttaacggcgaattttaacaaaaatataaacgttttac
aat

FIG. 13E

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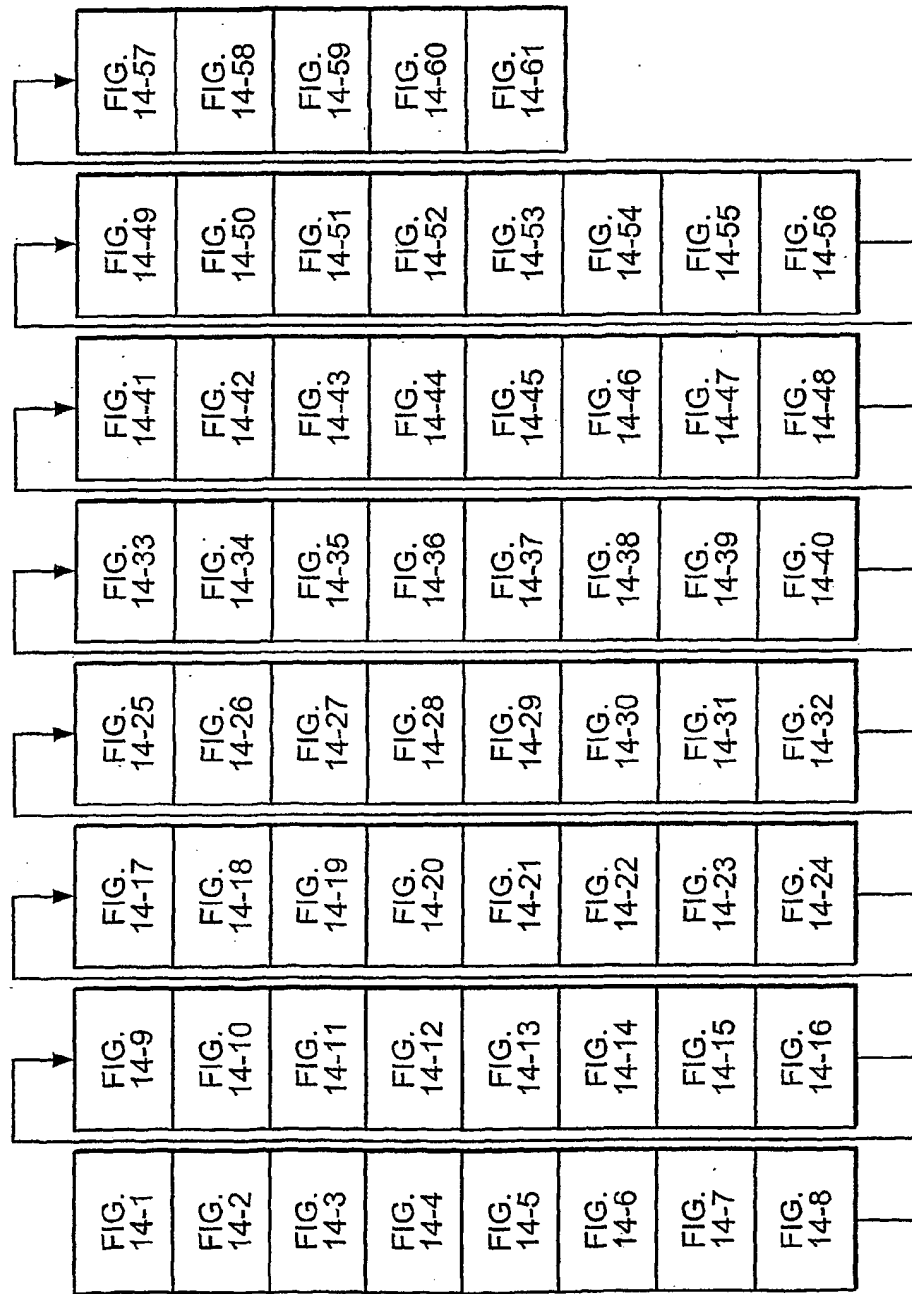


FIG. 14

pFLAG-CMV-5b-HDAC9a

7303 base pairs

<u>Graphic map</u>	<u>Table by enzyme name</u>
--------------------	-----------------------------

		BstMCI			
AviII	PvuI	BsiEI	EaRI	MspAII	
BglI	FspI	BsaOI	Eam1104I	PvuII	
ccattcgccattcaggctgcgcaactgttggaaggcgatcgggtcgggcctcttcgctattacgccagctgg					
base pairs					
gggtaagcgggtaagtcgacgcgttgacaaaccttcccgcctagccacgcccggagagcgataaatgcggtcgacc					
1 to 75					
Acc16I		BspCI		Ksp632I	NspBII
		Bsh1285I			
		Ple19I			

FIG. 14-1

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cgaaggggatgtgctgcaaggcgattaagtgggtaacgccagggtttcccagtcacgacgttgtaaaacg
base pairs
gctttccccctacacgacgttccgctaattcaaccattgcgggtcccaaaagggtcagtgctgcaacattttgc
76 to 150

MscI
CfrI

SspI MluNI

EaeI

acggccagtgccaagctgatctaataatcaataattggccattagccataattattcattggtatatagcataaaatcaa
base pairs
tgccgggtcacgggttcgactagattagttataaccgggtaatcgggtataataagtaaccaatataatcgtagtttagtt
151 to 225

EaeI
BamI

CfrI

FIG. 14-2

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MscI		
MluNI		
SspI	EaeI	BsrDI
		SspBI
		Bsp1407I
tattggctattggccattggcatagcgttgatccatatcataaatatgtacatttataattggctcatgtccaacatt		
base pairs		
ataaccgataaccggtaacgtatgcaacataggtagtattatacatgtataataaccgagtagcgggttgtaa		
226 to 300		
CfrI		BsrGI
BalI		

		VspI
HincII	SpeI	PshBI
accgccatgttgacattgattattgactagttatttaataagtaataatcaattacggggtcattagttcatagcccata		
base pairs		
tggcggtaacaactgtaactaataactgatcaataattatcattagttaatgccccagtaatacaagtatcgggtat		
301 to 375		
HindII	AclNI	AsnI
		AseI

FIG. 14-3

HinII
AcyI
HincII

BstMCI
BglI BsaOI

tatggagttccgcgttacataacttacggttaaatggcccgctggcgacgccccagcgacccccccggttgacg
base pairs
atacctcaaggcgcaatgtattgaatgccatttacccggcggaacgctggcggtcgctggggcggaactgc
376 to 450

HindII
Hsp92I
Msp17I

Bsh1285I
BsiEI

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BsaHI
AatII
BbiII

BbiII
HinII
AcyI AatII

tcaatagtgacgtatgttcccatagtaacgccaatagggaactttccattgacgtcaatgggtggagtatttacgg
base pairs
agttatcactgcatacaagggtatcattgcggttatccctgaaaggtaactgcagttaccacctcataaatgcc
451 to 525

Msp17I
BsaHI
Hsp92I

FIG. 14-4

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<p>BglI</p> <p>taaactgcccaacttggcaggtacatcaagtgtatcatatgcccaagtcgcgccccctattgacgtcaatgacggtaaa base pairs</p> <p>attgacgggtgaaccgtcatgtagtccacatagtatacggttcaggcgggggataaactgcagttactgccattt 526 to 600</p>	<p>NdeI</p>	<p>BbiII</p> <p>HinII</p> <p>AcyI AatII</p>
<p>FauNDI</p>	<p>Msp17I</p> <p>BsaHI</p> <p>Hsp92I</p>	
<p>tgccccgcctagcattatgccccaggtacatgaccttacgggagtttcctacttggcagttacatctacgtattagtc base pairs</p> <p>accgggaggatcgtaatacgggtcatgtactggaatgccctcaaaggatgaaccgtcatgtagatgcataatcag 601 to 675</p>		<p>BstSNI</p> <p>SnaBI</p> <p>BsaAI</p> <p>Eco105I</p>

FIG. 14-5

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NcoI Bsp19I
 StyI BstDSI
 EcoT14I
 atcgctattaccatgggtgatgcggttttggcagtagacacaaatgggcgtgtagcgggttgactcacggggattt
 base pairs
 tagcgataatggtaccactacgccaacacgtcatgtggttaccgcacacctatcgccaaactgagtgcacctaaa
 676 to 750
 BssT1I
 ErhI Eco130I
 DsaI MslI
 BblII
 HinII
 AccB1I
 AclI AatII
 BshNI
 ccaagtctccacccattgacgtcaatgggagttgttttggcaccacaaatcaacgggactttccaaaaatgtcgt
 base pairs
 gggtcagaggtgggtaactgcagttaccctcaaaacacacgtggttttagttgcccctgaaagggttttacagca
 751 to 825
 Msp17I
 BsaHI
 Hsp92I
 BanI
 Eco64I

FIG. 14-6

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HincII
 Eco24I
 EcoICRI
 aataacccgccccgttgacgcaaatgggaggtaggcgtgtacgggtgggaggtctatataagca gagctcgttta
 base pairs
 ttattgggcggggcaactgcgtttaccgcccatccgcacatgccaccctccagatatattcgt ctcgagcaaat
 826 to 900
 HindII
 Ecl136II
 Bbv12I
 AspHI
 Psp124BI

SacI
 FrlOI
 SstI
 BanII
 BsiHKAI
 AcsI
 ApoI
 BstZI
 BstMCI
 MflI
 Bsa29I
 SfcI
 EagI
 XmaIII
 BstYI
 BspDI
 BcgI
 Eco32I
 CciNI
 Bsh1285I
 BstX2I
 BanIII
 PstI
 BclI
 Ksp22I
 gtgaaccgtcagaattcaagcttgccgcccagatctatcgatctgcaggatatcaccatgcacacagtatgatcag
 base pairs
 cacttggcagtccttaagtctgaacgcccggcgtctagatagtagacgtccctatagtggtacgtgtcatactagtc
 901 to 975
 EcoRI
 EaeI
 Eco52I
 BglII
 BscI
 BspXI
 BstSFI
 CfrI
 EclXI
 BsiEI
 BseCI
 Bsu15I
 EcoRV
 NotI
 BsaOI
 XhoII
 ClaI
 Bsp106I
 FbaI
 Alw21I

FIG. 14-7

	FriOI	CvnI	CvnI
	ECO24I	AOCI	AOCI
	BpmI	Bsu36I	Bsu36I
ctcagtggtgaagtcagaagttcctgtgggcctggagcccatctcacctttagaccctaaggacagacctcag			
base pairs			
gagtcacctacacttcagtcctcaaggacacccggaccctcggttagagtggaatctggattcctgtctggagtc			
976 to 1050	GsuI	Eco8II	Eco8II
	BanII	Bse2II	Bse2II

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DsaI	DrdI	MfeI	Asp700I
gatgatgcccgtggtggaccctgttgtccgtgagaagcaattgcagcaggaattacttcttatccagcagca			
base pairs			
ctactactacgggcaccacacctgggacacacaggcactcttcgttaacgctcgtcccttaatgaagaataggctcgtcgt			
1051 to 1125	BstDSI	MunI	XmnI

FIG. 14-8

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AlwNI
gcaacaaatccagaagcagcttctgatagcagagtttcagaaacagcatgagaacttgacacggcagcaccaggc
base pairs
cgttggttaggtcttcgtcgaagactatcgtctcaaagtctttgtcgtaactcttgaaactgtgccgtcgtggtccg
1126 to 1200

BlpI
CellII Eco57I
tcagcttcaggagcatatcaaggaaacttctagccataaaacagcaacaagaactcctagaaaaggagcagaaaact
base pairs
agtcgaagtcctcgtatagttccttgaagatcgggtattttgtcgtttgttcttgaggatcttttcctcgtcttga
1201 to 1275
Bsp1720I
Bpu1102I

FIG. 14-9

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BpmI
BseRI
ggagcagcagaggcaagaacaggaagtagagaggcatcgagagaaacagcagcttcctcctctcagagggcaaaga
base pairs
cctcgtcgtctccggttcttgttccttcattctcctcgtagcgtctcttgcgcgaaggagagagtcctccggtttct
1276 to 1350
GsuI
EcoNI

HindIII
tagaggacgagaaaggcagtggaagtagacagaagtaaacag aagcttcaagagttcctactgagtaaatcagc
base pairs
atctcctgctctttcccggtcaccggttcattgtcttcatttcgtc ttcgaagttctcaaggatgactcatttagtcg
1351 to 1425

FIG. 14-10

Van91I
AccB7I
aacgaaagacactccaactaatggaaaaaatcattccgtgagccgccatcccaagctctggtacacggctgcccc
base pairs
ttgcttttctgtgaggttgattaccttttttagtaaggcactcggcggtagggttcgagaccatgtgccgacgggt
1426 to 1500

Van91I
AccB7I
ccacacatcattggatcaaaagtctccacccttagtggaacatctccatccctacaagtacacattaccaggagc
base pairs
ggtgtgtagtaacctagtttcgagaggtggggaatcaccttgtagaggtaggatgttcattgtgtaattggtcctcg
1501 to 1575

Esp1396I
PflMI
123/173

FIG. 14-11

124/173

Alw21I	BstBI	
AspHI	Bpu14I	FriOI
	Csp45I	Eco24I
acaagatgcaaaaggatgatttcccccttcgaaaaactgcctctgagcccaacttgaaggcggtccagggttaa		
base pairs		
tgttctacgttttccctactaaaggggaagctttttgacggagactcgggttgaacttccacgccagggtccaattt		
1576 to 1650		
BsiHKA I	SfuI	BanII
Bbv12I	Bsp119I	
	NspV	
	LspI	

	BseRI	EcoNI
acagaaagtggcagagaggagaagcagagcccttactcaggcggaaggatggaatgtgtcacttcattcaagaa		
base pairs		
tgtctttcaccggtctctccttctcgtcggggaatgagtcgcccttcctacctttacaacagtgaagtaagtctt		
1651 to 1725		

FIG. 14-12

Van91I
 AccB7I
 BpmI PflMI
 Van91I
 AccB7I
 gcgaatgtttgaggtgacagaatcctcagtcagtcagtagcagttctccaggctctgggccaggttcaccaacaatgg
 base pairs
 cgcttacaactccactgtcttaggagtcagtcagtcaggtccgagaccagggccaagtgggtttgttacc
 1726 to 1800
 GsuI
 Esp1396I
 PflMI
 125/173
 AlwNI
 Esp1396I

gccaaactggaagtgttactgaaaatgagacttcgggtttgccccctaccctcatgccgagcaaatgggttcaca
 base pairs
 cggttgaccttcacaatgacttttactctgaagccaaaacgggggatggggagtagcggtcgtttaccacaagtgt
 1801 to 1875

FIG. 14-13

BsaMI
Mva1269I
gcaacgcatttctaattcatgaagattccatgaacctgctaagtccttatacctctccttcttgcacattac
base pairs
cgttgcgtaagattaagtacttctaaggtagtgacgattcagaaatatggagaggaacgggttgtaatg
1876 to 1950

BsmI RcaI
BspHI

ErhI
BstT1I

BstBI Acsi
Bpu14I
Csp45I

126/173

cttgggggttcccgcagtgccatcccagctcaatgctc gaattcactcaaaagcagaagtggtgagacgca
base pairs
gaaccccgaaggcggtcacggtagggtcgagttacgaag ctttaagtgagtttcttcttcgtcttcacactctgcgt
1951 to 2025
EcoT14I

Esp3I

StyI
Eco130I

SfuI Bsp119I

NspV ApoI
LspI EcoRI

BsmBI

FIG. 14-14

127/173

gacgcttaggcaaggtgttcctctgcctgggcagtatggaggcagcatcccggcatcttccagccaccctcatgt
base pairs
ctgcgaatccggttcacaaggagacggaccggtcatcacctccgtcgtagggccgtagaaggtcggtgggagtaca
2026 to 2100

MslI

PstI

SfiI

taçtttagagggaaagccaccacaacagcagccaccagggtctc ctgcagcatttattattgaaagaacaatgcg
base pairs
atgaaatctccctttcgggtgtcgtcgggtccgagag gacgtcgtataataaactttcttgtttacgc
2101 to 2175

BstSFI

FIG. 14-15

128/173

Eco130I
 StyI
 EcoT14I
 ApoI
 HindIII
 acagcaaaagcttcttgtagctggtgagttcccttacatcctcagtcctcccttggaacaaagagagaatttc
 base pairs
 tgtcgttttcgaagaacatcgaccacctcaagggaatgtaggagtcagagggaaaccgttggtttctctcttaaag
 2176 to 2250
 BssT1I
 ErhI
 AcsI

Asp718I
 Acc65I
 BshNI
 BsgI
 acctggcattagaggtacccacaaaattgccccgtcacagacccctgaaccgaaccagctctgcacctttgcctca
 base pairs
 tggaccgtaatctccatgggtgtttaacgggggcagtgctgtgggacttggtcagacgtggaaacggagt
 2251 to 2325
 BanI
 KpnI
 ACCB1I
 Eco64I

FIG. 14-16

129/173

Bpu1102I
 Alw21I Bsp1720I
 AspHI CelII
 gagcacgttggctcagctggtcattcaacagcaacaccagcaattcttggagaagcagaagaataaccagcagca
 base pairs
 ctcgtagcaaccgagtcgaccagtaagtgtcggtcggttaagaacctcttcgtcttcggttatgggtcgtcgt
 2326 to 2400
 BsiHKAI PvuII
 Bbv12I BlnI MspAII
 NspBII
 MflI
 XhoII
 gatccacatgaacaaactgcttttcgaaatctattgaacaaactgaagcaaccaggcagtcaccttgaggaagcaga
 base pairs
 ctagggtgtacttgtttgacgaaagctttagataaacttggtgacttcggttggtccgtcagtggaactccttcgtct
 2401 to 2475
 BstYI
 BstX2I
 BstBI
 Bpu14I
 Csp45I
 Eco57I
 SfuI Bsp119I
 NspV
 LspI

FIG. 14-17

130/173

EarI	Bbv16II
Eam1104I	BbsI
Asp700I	Bsp143II

ggaagagcttcaggggaccaggcgatgcaggaagacagagcgccctctagtggcaacagcactaggagcgacag
 base pairs
 ccttctcgaagtccccctgggtccgctacgtccttctgtctcgcgggagatcacccgttgctcgatcctcgtgtc
 2476 to 2550

XmnI	Eco57I	BpiI	HaeII
Ksp632I		BpuAI	BstH2I
SapI			

BcgI

cagtgtgtgtggatgacacactgggacaagtggggctgtgaagggtcaaggagggaaccagtggaacagtgatga
 base pairs
 gtcacgaacacacactactgtgtgaccctgttcaacccccgacacttccagttcctccttggtcacctgtcactact
 2551 to 2625

FIG. 14-18

MflI Van91I
 XhoII AccB7I
 agatgctcagatccaggaaatggaatctggggagcaggctgttttatgcaacagcctttcctggaacccacgca
 base pairs
 tctacgagtcctaggtcctttaccttagacccctcgccgacgaaatacgttgctcgaaaggaccttgggtgcgt
 2626 to 2700
 BstYI Esp1396I
 BstX2I PflMI

131/173

PmaCI
 PmlI
 AflIII NspBII
 cacacgtgcgctctctgtgcgccaagctccgctggctgcggttgccatggatggattagagaacacccgtctcgt
 base pairs
 gtgtgcacgcgagagacacgcggttcgaggcgaccgacgccaaccgtacctaatctcttggcagagca
 2701 to 2775
 MslI Eco72I MspAII
 BsaAI
 BbrPI BsmBI

FIG. 14-19

132/173

EarI	BpmI	BsrDI	BpmI
Eam1104I			
ctccaggactcactcttcccctgctgcctctgttttacctcaccagcaatggaccgccccctccagcctggctc			
base pairs			
gaggtcctgagtgagaaggggacgacggagagacaaaaatggagtgggtcggttacctggcgggggaggtcggaccgag			
2776 to 2850			
GsuI	Ksp632I		GsuI

	XcmI
tgcaactggaattgcctatgaccccttgatgctgaaacaccagtgcgtttgtgggaattccaccaccacctga	
base pairs	
acgttgaccttaacggatactggggaactacgactttgtggtcacgcaaacacccgttaagggtgggtgggact	
2851 to 2925	

FIG. 14-20

133/173

SphI
 BbuI
 AclI
 AclI
 gcatgctggacgaatacagagtagtctgggtcacgactgcaagaactgggctgctaaataaatgtgagc gaattca
 base pairs
 cgtacgacctgcttatgtctcatagaccagtgtgacgttctttgacccgacgatttatttactactcg ctttaagt
 2926 to 3000
 PaeI
 NspI
 EcoRI

AccBII
 BshNI
 aggtcgaaaagccagcctggaggaatacacagcttggttcattctgaacatcactcactgttgtagtggaaccaacc
 base pairs
 tccagcttttcggtcggacctcctttatgtcgaacaagtaagacttgtagtgagtgacaacataccgtggttggg
 3001 to 3075
 GsuI
 BanI
 Eco64I

FIG. 14-21

134/173

ErhI
StyI Eco130I
EcoT14I
BstXI AlwNI
cctggacggacagaagctggaccccaggatactcctaggtgatgactctcaaaagttttttccctcattaccttg
base pairs
ggacctgcctgtcttcgacctggggtcctatgaggatccactactgagagttttcaaaaaaggagtaatgggaac
3076 to 3150

BstT1I
AvtII
BlnI

BsaWI BsgI
tggtggacttggggtggacagtgacaccatttggaatgagctacactcgtccggtgctgcacgcgtggttgg
base pairs
accacctgaacccccacctgtcactgtggtaaaccttactcgtgtgagcagggccacgacgtgctaccgacaacc
3151 to 3225

FIG. 14-22

CvnI	CfrI
AocI	DraII EaeI
Bsu36I	Eco57I

ctgtgtcatcgagctgggttccaaagtggcctcaggagagctgaagaatgggtttgctgtgtgagggcccttg
base pairs

gacacagtagctcgaccgaaggtttcaccggagtcctctcgacttcttacccaaacgacaacactccgggggacc
3226 to 3300

Eco81I Eco0109I
Bse21I

135/173

MscI	ErhI Eco130I
	BssT1I BstXI
	Eco57I MslI DsaI

ccatcacgctgaagaatccacagccatgggggttctgcttttttaattcagttgcaattaccggccaaatcttgag
base pairs

ggtagtgcgacttcttaggtgtcggtaccccaagacgaaaaaattaagtcaacgttaatggcggtttatgaactc
3301 to 3375

MluNI EcoT14I
Bali StyI BstDSI
NcoI Bsp19I

FIG. 14-23

BstX2I	NcoI	Bsp19I	Asp718I	SseBI
BstYI	StyI	BstDSI	AccB1I	
	XhoII	ECO14I	BshNI	StuI
	BsaI			
		agaccaaactaaataataagcaagataattgattgtagatctggatgttcaccatggaaacgggtaccacagcagcctt		
		base pairs		
		tctgggttgatttatattcgttctataactaacatctagacctaacaagtggtagccttggccatgggtcgtccggaa		
		3376 to 3450		
	Eco31I		BglII	BstT1I
			MflI	ErhI
				Eco130I
				DsaI
				Acc65I
				AatI
				Pme55I

SspBI			
BspI407I	MslI	Asp700I	
ttatgctgacccagcatcctgtacatttca	ctccatcgctatgatgaagggaactttt	ccctggcagtgga	
base pairs			
aatagcactggggtcgtaggacatgtaaagt	gaggtaggatatactacttcccttgaaaaagg	accgtcacctcg	
3451 to 3525			
BsrGI		XmnI	

FIG. 14-24

Acc65I
 BanI Eco64I
 BstX2I Asp718I
 cggtagcagattacaaggacgacgatgacaaagtagat ccgggtggcatccctgtgacccctcccagtgccctct
 base pairs
 gccatgggtctaattgttcctgctgctactgttcatcta gggcccaccgtagggacactggggagggtcacggaga
 3601 to 3675
 BshNI
 BsaWI KpnI
 AccBI
 BstYI Ama87I
 BstX2I BsoBI
 XmaI PspAI
 137/173
 BstYI
 XhoII
 BsrDI
 cccaaatgaggttcggttatttcttagagccccacttttatttgtatctttcaggttaattgcattgca ggatc
 base pairs
 gggtttactccaagccaaataaagaaatctcgggtgaaaataaacatagaaagtcattaaacgtaacgt cctag
 3526 to 3600
 BanII
 BanHI
 BstI
 MflI

FIG. 14-25

138/173

Eco130I	GsuI				
StyI				SfcI	Bbv16II
EcoT14I	MslI			DraII BanII	BbsI
				PspOMI FrioI	
cctggccttggaagtggccactccagtgcccaccagccttgctcctaataaaattaagttgcatcattttgtctga					
base pairs					
ggac'cggaaccttcaacggtgaggtcacgggtggtcggaacaggattattttaattcaacgtagtaaaacagact					
3676 to 3750					
BssT1I	BpmI			Eco24I	
ErhI					
Eam1105I	SspI				
AspEI					
ctagggtgcctctataataattatgggtggaggggggtggtatggagcaagggggcccaagttgggaagacaacct					
base pairs					
gatccacaggagatatataataccccacctccccccaccataacctcgttccccgggttcaaaccttctgttgga					
3751 to 3825					
EclHKI	Bsp120I				BpiI
AhdI	EcoO109I				BpuAI
	Apal				BstSFI

FIG. 14-26

DraII	BpmI BsgI	
gtagggcctgcggtctattcgggaaccaagctggagtgagtggcacaatcttggtcactgcaatctccgcc		
base pairs		
catccggacgccccagataagcccttggttcgacctcacgtcacgtgttagaaccgagtgacgttagagggcgg		
3826 to 3900		
EcoO109I	GsuI	
		139/173
	BcoI	NspI BlpI
	Ama87I	PaeI Mph1103I
	BcgI	Ppu10I EcoT22I
tcctgggttcaagcgaattctcctgcctcagcctcccagttgttggtccaggcatgaccaggctcagc		
base pairs		
aggacccaagtctcgctaagaggacggagtcggagggctcaacaaccctaagggtccgtactggtccgagtcg		
3901 to 3975		
	Eco88I	BbuI Zsp2I CelII
	BsoBI	SphI Bsp172
		NsiI BpuII

FIG. 14-27

BbiII NcoI Eco130I BsrFI PflMI
 HinII StyI DsaI AgeI Bse118I
 DraI AclI AatII BsaWI AccB7I
 ttaaaataactataaccagcaggagcgtccagacacagcataggctacctgccatggcccaaccgggtgggacat
 base pairs
 aattttattgatatgggtcgtccctcctcctgcaggtctgtgtcgatccgatggacgggtaccgggtggccaccctgta
 4126 to 4200
 Msp17I BssAI Esp1396I
 BsaHI ErhI BstDSI PinAI Van91I
 Hsp92I BspMI Bsp19I Cfr10I

141/173

EaeI
 ttgagttgcttgcttggaactgtcctctcatgcgttgggtccactcagtagatgcctgttggaattgggtacgcgg
 base pairs
 aactcaacgaacgaaccgtgacaggagagtagcgaacccagggtgagtcctacggacaacttaaccatgcgcc
 4201 to 4275
 CfrI

FIG. 14-29

142/173

AlwNI
ccagcttctgtggaatgtgtgcagttaggtgtggaagtccccagggtccccagcaggcagaagtatgcaaag
base pairs
ggtcgaagacaccttacacacagtcattccacacacctttcaggggtccgaggggtcggtcgtcttcatacgttttc
4276 to 4350

NspI
PaeI Mph1103I
Ppu10I EcoT22I SexAI
catgcatctcaattagtcagcaaccagggtgtggaagtccccagggtccccagcaggcagaagtatgcaaagca
base pairs
gtacgtagagtttaatacagtcgttggtccacaccttttcaggggtccgaggggtcggtcgtcttcatacgttttcgt
4351 to 4425
BbuI Zsp2I
SphI
NsiI

FIG. 14-30

143/173

```

NspI
PaeI Mph1103I
Ppu10I EcoT22I
tgcatctcaattagtcagcaaccatagtcgcccccctaactccgcccataccgcccctaactccgcccagttccg
base pairs
acgtagagttaatcagtcggttggtatcagggcggggattgagggcgggtagggcggggattgagggcgggtcaaggc
4426 to 4500
BbuI Zsp2I
SphI
NsiI

NcoI Bsp19I
StyI BstDSI
EcoT14I
ccattctccgcccattggctgactaatTTTTTTTatttatgcagagggcggcctcggcctctgagctat
base pairs
gggtaagagggcggtaccgactgattaaaaaaaaataacgtctcggctccggcgaggccggagactcgata
4501 to 4575
BstT1I
ErhI Eco130I
DsaI
SfiI

```

FIG. 14-31

144/173

SseBI	AvrII	Ama87I
Eco147I	BlnI	Eco88I
StuI	BsSTI	AvaI
BseRI		BsoBI

tccagaagtagtgaggaggttttttggaggcctaggcttttgcaaaaagctc ctcgaggaaactgaaaaaccaga
base pairs
aggtcttccatcactcctccgaaaaaacctccggatccgaaaaacgttttttcgag gagctccttgacttttttggtct
4576 to 4650

AatI	StyI	XhoI	BcoI
Pme55I	ErhI	Sfr274I	
EcoT14I	Eco130I	PaeR7I	

SfcI	ApoI
------	------

aagttaattccctatagtgagtcgtatttaaattcgtaatcatggtcatagctgtttcctgtgtgaaattgtttatc
base pairs
ttcaattaagggatcactcagcataatttaagcatttagtaccagtatcgacaaaaggacacactttaacaatag
4651 to 4725

BstSFI	AcsI
--------	------

FIG. 14-32

AccBSI
 BsrBI
 cgctcacaaattccacacaacatacgagccggaagcataaagtgtaaagcctgggggtgcctaataatgagtgcgtaaac
 base pairs
 gcgagtgttaaggtgtgtgtatgctggccttcgtatttcacatttcggacccccacggattactcactcgattg
 4726 to 4800
 BstD102I
 AccB1I
 BshNI
 BanI
 Eco64I

145/173

VspI
 PshBI
 VspI
 MspA1I
 PvuII PshBI
 EaeI
 tcacattaattgcgctcactgcccgcttccagtcgggaaacctgtcgtgccagctgcattaatgaatcg
 base pairs
 agtgaattaacgcaacgcgagtgacgggcgaaaggcagccctttggacagcacgggtcgacgtaattacttagc
 4801 to 4875
 AsnI
 AseI
 NspBII
 CfrI
 AsnI
 AseI

FIG. 14-33

146/173

Eam1104I
BstH2I
Bsp143II
gccaacgcgcgagggttgcggtattggggcgctcttcggcttcctcgctcactgactcgctgcgctcgg
base pairs
cggttgcgcgccccctctccgccaaacgcataaacccgcgagaaaggagcgagtgactgagcgacgcgagcc
4876 to 4950
HaeII EarI
SapI
Ksp632I

BstMCI
 BsaOI
 base pairs
 agcaagccgacgcgctcgccatagtcgagtgagttccgccattatgccaatagggtgtcttagtccccctattgc
 4951 to 5025
 Bsh1285I
 BsiEI
 AccBSI
 BsrBI
 tcgttcggctgcgcgagcgggtatcagctcactcaaaaggcggtaatacggttatccacagaatcaggggataacg

FIG. 14-34

147/173

NspI
BspLU11I
caggaaagaacatgtgagcaaaaggccagcaaaaggccaggaaacgtaaaaaggccgcttgctggcgtttttcc
base pairs
gtcctttcttgtaactcgttttccggtcgtttccggtccttggcattttccggcgcaacgacccgcaaaaagg
5026 to 5100
AflIII

DrdI
ataggctccgccccctgacgagcatcacaaaaatcgacgctcaagtcagaggtggcgaaacccgacaggactat
base pairs
taccgaggcggggactgctcgtagtgttttagctcgagttcagtcctccacggctttgggctgtcctgata
5101 to 5175

FIG. 14-35

148/173

BsiI BsaWI
aaagataccaggcgtttccccctggaagctccctcgtgcgctctcctgttccgaccctgccgcttaccggatacc
base pairs
tttctatggtccgcaaaaggggaccttcgaggagcacgcgagaggaagaaggctgggacggcggaatggcctatgg
5176 to 5250

BssSI

BstH2I Bsp143II SfcI
tgtccgcctttctcccttcgggaagcgtggcgctttctcaatgctcacgctgtaggtatctcagttcgggtgtagg
base pairs
acaggcggaagagggaagcccttcgcaccgcgaaagagttacgagtgcgacatccatagagtcgaagccacatcc
5251 to 5325

HaeII BstSFI

FIG. 14-36

AlwNI
gtcttgagtccaacccggtaagacacgacttatcgccactggcagcagccactggtaacaggattagcagagcga
base pairs
cagaactcagggttggggcattctgtgctgaatagggtgaccgtcgtcggtgaccattgtcctaatcgtctcgcct
5401 to 5475

FIG. 14-37

150/173

Sfcl
 ggtatgtaggcggtgctacagagttcttgaagtggcctaactacggctacactagaagaacagtatttggta
 base pairs
 ccatacatccgcccacgatgtctcaagaacttcaccaccggattgatgccgatgtgatcttcttgcataaacat
 5476 to 5550

BstSFI

Eco57I
 NspBII
 tctgcgctctgctgaagccagttaccttcggaaaaagagttggtagctcttgatccggcacaacacccgctg
 base pairs
 agacgcgagacgacttcggtcaatggaagccttttctcaaccatcgagaactaggccgttctgttggggcgac
 5551 to 5625
 MspAII

FIG. 14-38

	MfII	MfII
	XhoII	XhoII
gtagcggtaggtttttgttgcaagcagcagattacgcgcagagaaaaaaggatctcaagaagatcctttgatct		
base pairs		
catcgccacccaaaaaacaacgttcgtcgtctaatacgcgctcttttttccctagagttcttctaggaactaga		
5626 to 5700		
	BstXI	BstXI
	BstX2I	BstX2I

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	RcaI	MfII
		XhoII
tttctacgggtctgacgctcagtggaacgaaaactcacgttaagggttttggtcatgagattatcaaaaagga		
base pairs		
aaagatgccccagactgcgagtcaccttgcttttgagtgcgaattccctaaaaccagtactctaatagtttttcct		
5701 to 5775		
	BspHI	BstXI
		BstX2I

FIG. 14-39

152/173

MflI DraI
XhoII DraI
tcttcacctagatcccttttaaattaaaaatgaagttttaaatcaatcctaagtatatatgagtaaacttgggtctg
base pairs
agaagtggatctaggaaaatttaatttttacttcaaaaatttagttagatttcatatatactcatttgaaccagac
5776 to 5850
BstYI
BstX2I

AccB1I
BshNI
acagttaccaatgctttaatcagtgaggcacctatctcagcgatctgtctatttcgttcatccatagttgcctgac
base pairs
tgtcaatgggttacgaaattagtcactccgtggatagatcgctagacagataaagcaagtaggtatcaacggactg
5851 to 5925
BamI
Eco64I

FIG. 14-40

153/173

Eam1105I
AspEI
BsrDI
tccccgtcgtgtagataaactacgatacgggagggttaccatctggcccagtgctgcaatgataccgagagacc
base pairs
aggggcagcacatctattgatgctatgccctcccgaatggtagaccgggtcacgacgttactatggcgctctggg
5926 to 6000
EclHKI
AhdI

Cfr10I
BsaI BssAI BpmI BglI
cacgtcacccggctccagatttatcagcaataaaccagccggaaggccgagcgagaagtggctcctgcaa
base pairs
gtgcgagtggccgaggtctaaatagtcgttatttggtcggtcggccttcccggctcgcgtcttcaccaggacgtt
6001 to 6075
Eco31I BsrFI GsuI
Bse118I

FIG. 14-41

154/173

VspI
PshBI
ctttatccgcctccatccagtcctataattgttgccgggaagctagagtaagtagttcgccagttaatagtttgc
base pairs
gaaataggcgggtaggtcagataattaacaacggcccttcgatctcattcatcaagcgggtcaattatcaaacg
6076 to 6150
AsnI
AseI

AviII
FspI
gcaacggtgttgccattgctacaggcatcggtgtcacgctcgctgttggtatggcttcattcagctccggtt
base pairs
cgttgcaacaacggtaacgatgtccgtagcaccacagtcgagcagcaaacccataccggaagtaagtcgaggccaa
6151 to 6225
Acc16I
BsrDI
Psp1406I
BstSFI
SfiI
MslI
BsaWI

FIG. 14-42

BsiEI
PvuI
BstMCI
BsaOI

cccaacgatcaaggcgagttacatgatcccccatgttggtgcaaaaaagcggtagctccttcggtcctccgatcg
base pairs
gggttgctagttccgctcaatgtactaggggtacaacacgtttttcgccaatcgaggaagccaggaggctagc
6226 to 6300

BspCI
Bsh1285I
Ple19I

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MslI

EaeI

ttgtcagaagtaagttggccgcagtggttatcactcatgggttatggcagcactgcataattcttactgtcatgc
base pairs
aacagtccttcattcaaccggcggtcaccaatagtgagtaccaataaccgtcgtgacgtattaagagaatgacagtagc
6301 to 6375

CfrI

FIG. 14-43

Acc113I	BstMCI	
Eco255I	BsaOI	
catccgtaagatgcttttctgtgactgggtgagtactcaaccaagtcattcttgagaatagtgatcgggcgaccga		
base pairs		
gtaggcattcttacgaaaaagacactgaccactcatgagttgggttcagtaagactcttatacacatacgccgctggct		
6376 to 6450		
ScaI	Bsh1285I	
	BsiEI	
BbiII		156/173
HinII	Alw21I	
BcgI	AspHI	
gttgctcttgcccggtcaatacgggataataccgcgccacatagcagaactttaaaagtgtcatcattggaa		
base pairs		
caacgagaacggggccgcaggttatgccctattatggcgcggtgtatcgctcttgaaattttcacgagtagtaacctt		
6451 to 6525		
Msp17I	BsiHKAI	
BsaHI	Bbv12I	
Hsp92I		

FIG. 14-44

XmnI

Psp1406I

aacgttcttcggggcgaaaactctcaaggatcttacggctgttgagatccagttcgcgtgatgtaacccactcgtgcac

base pairs

ttgcaagaagccccgcttttgagagttcctagaatggcgacaactctaggtcaagctacattggggtgagcacgtg

6526 to 6600

Asp700I

MflI

XhoII

NspBII

XhoII

MflI

BssSI

Alw44I

VneI

BstYI

BstX2I

MspAII

BstYI

BstX2I

ApalI

BsiI

AspHI

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Bbv12I

BsiHKAI

ccaaactgatcttcagcatcttttactttcaccagcgtttctgggtgagcaaaaaacaggaaggcaaaatgccgcaa

base pairs

ggttgactagaagtcgtagaaaaatgaaagtgggtcgaaagaccactcgtttttgtccttccggttttacggcggtt

6601 to 6675

Alw21I

Eco57I

FIG. 14-45

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MslI EarI SspI
 aaaaggaataagggcgacacgggaaatggtgaatactcatactcttccttttcaatatattgaagcatttattc
 base pairs
 tttcccttattcccgctgtgcctttacaacttatgagtatgagaagggaaaaagtataataacttcgtaaatag
 6676 to 6750
 Ksp632I

AccBSI RcaI BsrBI
 agggttattgtctcatgagcggatacatatttgaatgtatttagaaaaataaacaataaggggttccgcgcacat
 base pairs
 tcccaataacagagtagtccgctatgtataaaacttacataaatctttttattgtttatccccaaggcgcgtgta
 6751 to 6825
 BspHI BstD102I

FIG. 14-46

SfcI

ttccccgaaaagtgccacacctgacggcgccctgtagcggcgcatattaagcggcggggtgtggttggttacgcgcagcgg
 base pairs
 aaggggcttttcacgggtggactgcgcgggacatgcgcgcgtaattcgcgcgcgccacacacccaatgcgcgtcgc
 6826 to 6900

BstSFI

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BsrFI
 BssAI
 MroNI

AccBSI
 BstH2I HaeII BstD102I
 Bsp143II BsrBI

tgaccgctacacttgccagcgccctagcggccgctcctttcgcgtttcctcccttctcctccacggttcgcgcg
 base pairs
 actggcgatgtgaacgggtcgcgggacgcgggcgaggaagcgaagaaagggaagagcgggtgcaagcggc
 6901 to 6975

HaeII Bsp143II
 BstH2I

NgoAIV
 NgoMI
 Bse118I

FIG. 14-47

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NaeI
gctttcccggtcaagctctaaatcggggcatccctttagggtccgatttagtgctttacggcacctcgacccca
base pairs
cgaaggggcagttcgagatttagccccgtagggaaatcccaaggctaaatcacgaaatgccgtggagctgggggt
6976 to 7050

AccBII
BshNI

BanI
Eco64I

Cfr10I

BsaAI
aaaaacttgattagggtgatggttcacgtagtggggccatgccctgatagacgggtttttcgccctttgacgttgg
base pairs
tttttgaactaatcccactaccaagtgcatacccggtagcgggactatctgccaaaaagcgggaaactgcaacc
7051 to 7125

DraIII

FIG. 14-48

agtcacggttctttaatagtggaactctgttccaactggaacaacactcaaccctatctcgggtctattcttttg
base pairs
tcaggtgcaagaattatcacctgagaacaagggttgaccttggtgtgagttgggatagagccagataaagaaaac
7126 to 7200

atttataagggattttgccgatttcggcctatttggttaaaaaatgagctgatttaacaaaaatttaacgcgaatt
base pairs
taaataatcccctaaaaacgggctaagccggataaccaattttttactcgactaaattgtttttaaatggcgcttaa
7201 to 7275

ApoI ApoI

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Acsi Acsi

SspI Psp1406I
ttaacaaaaatattaaacggtttacaattt base pairs
aattgttttataaatttgcaaatgttaaa 7276 to 7303

FIG. 14-49

Table by Enzyme Name

Enzyme name	No. cuts	Positions of sites	Recognition sequence
AatI	2	3446 4606	agg/cct <u>More info</u>
AatII	5	451 504 587 773 4154	gacgt/c <u>More info</u>
Acc113I	1	6408	agt/act <u>More info</u>
Acc16I	2	21 6150	tgc/gca <u>More info</u>
Acc65I	3	2264 3434 3602	g/ gtacc <u>More info</u>
AccB1I	8	791 2264 3065 3434 3602 4779	g/ gyrcc <u>More info</u>
		5876 7036	
AccB7I	6	1445 1482 1775 1796 2644 4191	ccannnn/ntgg <u>More info</u>
AccBSI	4	4730 4971 6772 6936	
Ac1NI	1	326	gagcgg <u>More info</u>
AcSI	7	912 1990 2244 2994 4679 7260	a/ ctagt <u>More info</u>
		7271	r/ aatty <u>More info</u>
AcylI	6	448 501 584 770 4151 6465	gr/cgyc <u>More info</u>
Afl1III	2	2702 5035	a/ crygt <u>More info</u>
AgeI	1	4188	a/ ccggt <u>More info</u>
AhdI	2	3754 5928	gacnnn/ngtc <u>More info</u>
Alw21I	6	894 1576 2330 5353 6514 6599	gwgcw/c <u>More info</u>
Alw44I	2	5349 6595	g/ tgcac <u>More info</u>

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FIG. 14-50

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AlwNI	6	1147	1273	1775	3091	4282	5451	cagnnn/ctg	More info
Ama87I	3	3638	3934	4629				c/ ycgrg	More info
AocI	3	1034	1046	3256				cc/ tnagg	More info
Apal	1	3806						gggcc/c	More info
ApalI	2	5349	6595					g/ tgcac	More info
ApoI	7	912	1990	2244	2994	4679	7260	r/ aatty	More info
		7271							
AseI	4	334	4806	4865	6100			at/ taat	More info
AsnI	4	334	4806	4865	6100			at/ taat	More info
Asp700I	4	1107	2481	3506	6527			gaann/nnttc	More info
Asp718I	3	2264	3434	3602				g/ gtacc	More info
AspEI	2	3754	5928					gacnnn/nngtc	More info
AspHI	6	894	1576	2330	5353	6514	6599	gwgwc/c	More info
AvaI	3	3638	3934	4629				c/ ycgrg	More info
AviII	2	21	6150					tgc/gca	More info
AvrII	2	3109	4607					c/ ctagg	More info
BalI	4	184	238	3300	4018			tgg/cca	More info
BamHI	1	3596						g/ gatcc	More info
BanI	8	791	2264	3065	3434	3602	4779	g/ gyrcc	More info
		5876	7036						
BanII	6	894	1017	1623	3526	3558	3806	grgcy/c	More info
BanIII	1	939						at/ cgat	More info
BbiII	6	448	501	584	770	4151	6465	gr/cgyc	More info

FIG. 14-51

BbrPI	1	2705		cac/gtg	<u>More info</u>
BbsI	2	2512 3820		gaagac	<u>More info</u>
BbuI	4	2930 3959 4354 4427		gcatg/c	<u>More info</u>
Bbv12I	6	894 1576 2330 5353 6514 6599		gwgw/c	<u>More info</u>
Bbv16II	2	2512 3820		gaagac	<u>More info</u>
BcgI	4	941 2556 3925 6455		cgannnnntgc	<u>More info</u>
BclI	1	969		t/ gatca	<u>More info</u>
BcoI	3	3638 3934 4629		c/ ycgrg	<u>More info</u>
BglI	5	14 417 538 4560 6048		gccnnnn/nggc	<u>More info</u>
BglII	2	932 3409		a/ gatct	<u>More info</u>
BlnI	2	3109 4607		c/ ctagg	<u>More info</u>
BlpI	3	1200 2337 3970		gc/tnagc	<u>More info</u>
BpiI	2	2512 3820		gaagac	<u>More info</u>
BpmI	9	1015 1279 1772 2781 2842 3022		ctggag	<u>More info</u>
		3701 3863 6018			
Bpu1102I	3	1200 2337 3970		gc/tnagc	<u>More info</u>
Bpu14I	3	1603 1988 2423		tt/cgaa	<u>More info</u>
BpuAI	2	2512 3820		gaagac	<u>More info</u>
Bsa29I	1	939		at/ cgat	<u>More info</u>
BsaAI	3	666 2705 7077		yac/gtr	<u>More info</u>
BsaHI	6	448 501 584 770 4151 6465		gr/cgyc	<u>More info</u>

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FIG. 14-52

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BsaI	3	3380	4031	6000	ggtctc	More info
BsaMI	1	1886			gaatgc	More info
BsaOI	7	42	424	928 4951 5375 6298 6447	cgry/cg	More info
BsaWI	6	3200	3599	4188 5241 5388 6219	w/ ccgww	More info
BsCI	1	939			at/ cgat	More info
Bse118I	3	4188	6008	6972	r/ ccggy	More info
Bse21I	3	1034	1046	3256	cc/ tnagg	More info
BseCI	1	939			at/ cgat	More info
BseRI	4	1337	1671	4593 4631	gaggag	More info
BsgI	3	2315	3212	3868	gtgcag	More info
Bsh1285I	7	42	424	928 4951 5375 6298 6447	cgry/cg	More info
BshNI	8	791	2264	3065 3434 3602 4779	g/ gyrc	More info
		5876	7036			
BsiEI	7	42	424	928 4951 5375 6298 6447	cgry/cg	More info
BsiHKAI	6	894	1576	2330 5353 6514 6599	gwgcw/c	More info
BsiI	2	5213	6597		ctcgtg	More info
BsmBI	3	2023	2773	4001	cgtctc	More info
BsmI	1	1886			gaatgc	More info
BsoBI	3	3638	3934	4629	c/ ycgrg	More info
Bsp106I	1	939			at/ cgat	More info
Bsp119I	3	1603	1988	2423	tt/cgaa	More info
Bsp120I	1	3802			g/ ggccc	More info
Bsp1407I	2	270	3471		t/ gtaca	More info

FIG. 14-53

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Bsp143II	5	2519	4913	5283	6922	6930	rgcgc/y	<u>More info</u>
Bsp1720I	3	1200	2337	3970			gc/tnagc	<u>More info</u>
Bsp19I	5	686	3324	3424	4178	4514	c/ catgg	<u>More info</u>
BspCI	2	42	6298				cgat/cg	<u>More info</u>
BspDI	1	939					at/ cgat	<u>More info</u>
BspHI	3	1891	5755	6763			t/ catga	<u>More info</u>
BspLul1I	1	5035					a/ catgt	<u>More info</u>
BspMI	2	1913	4178				acctgc	<u>More info</u>
BspXI	1	939					at/ cgat	<u>More info</u>
BsrBI	4	4730	4971	6772	6936		gagcgg	<u>More info</u>
BsrDI	5	245	2827	3594	5987	6169	gcaatg	<u>More info</u>
BsrFI	3	4188	6008	6972			r/ ccggy	<u>More info</u>
BsrGI	2	270	3471				t/ gtaca	<u>More info</u>
BssAI	3	4188	6008	6972			r/ ccggy	<u>More info</u>
BssSI	2	5213	6597				ctcgtg	<u>More info</u>
BsST1I	11	686	1950	2226	3109	3324 3424	c/ cwwgg	<u>More info</u>
		3681	4060	4178	4514	4607		
BstBI	3	1603	1988	2423			tt/cgaa	<u>More info</u>
BstD102I	4	4730	4971	6772	6936		gagcgg	<u>More info</u>
BstDSI	6	686	1062	3324	3424	4178 4514	c/ crygg	<u>More info</u>
BstH2I	5	2519	4913	5283	6922	6930	rgcgc/y	<u>More info</u>
BstI	1	3596					g/ gatcc	<u>More info</u>

FIG. 14-54

BstMCI	7	42 424 928 4951 5375 6298 6447	cgry/cg	<u>More info</u>
BstSFI	8	944 2144 3824 4662 5300 5491	c/ tryag	<u>More info</u>
		6169 6854		
BstSNI	1	666	tac/gta	<u>More info</u>
BstX2I	12	932 2400 2634 3409 3596 3634	r/ gatcy	<u>More info</u>
		5676 5687 5773 5785 6553 6570		
BstXI	3	3076 3325 4077	ccannnnn/ntgg	<u>More info</u>
BstYI	12	932 2400 2634 3409 3596 3634	r/ gatcy	<u>More info</u>
		5676 5687 5773 5785 6553 6570		
BstZI	1	925	c/ ggccg	<u>More info</u>
Bsu15I	1	939	at/ cgat	<u>More info</u>
Bsu36I	3	1034 1046 3256	cc/ tnagg	<u>More info</u>
CciNI	1	925	gc/ggccgc	<u>More info</u>
CelII	3	1200 2337 3970	gc/tnagc	<u>More info</u>
Cfr10I	3	4188 6008 6972	r/ ccggy	<u>More info</u>
Cfr9I	1	3638	c/ ccggg	<u>More info</u>
CfrI	9	152 182 236 925 3298 4016 4273	y/ ggccr	<u>More info</u>
		4874 6316		
ClaiI	1	939	at/ cgat	<u>More info</u>
Csp45I	3	1603 1988 2423	tt/cgaa	<u>More info</u>
CvnI	3	1034 1046 3256	cc/ tnagg	<u>More info</u>

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FIG. 14-55

DraI	4	4127	5794	5813	6505	ttt/aaa	More info
DraII	3	3291	3802	3829		rg/gnccy	More info
DraIII	1	7080				cacnnn/gtg	More info
DrdI	3	1076	5143	7124		gacnnnn/nngtc	More info
Dsai	6	686	1062	3324	3424 4178 4514	c/ crygg	More info
EaeI	9	152	182	236	925 3298 4016 4273	y/ ggccr	More info
		4874	6316				
EagI	1	925				c/ ggccg	More info
Eam1104I	5	58	2482	2793	4918 6722	ctcttc	More info
Eam1105I	2	3754	5928			gacnnn/nngtc	More info
EarI	5	58	2482	2793	4918 6722	ctcttc	More info
Ecl1136II	1	892				gag/ ctc	More info
EclHKI	2	3754	5928			gacnnn/nngtc	More info
EclXI	1	925				c/ ggccg	More info
Eco105I	1	666				tac/gta	More info
Eco130I	11	686	1950	2226	3109 3324 3424	c/ cwwgg	More info
		3681	4060	4178	4514 4607		
	2	3446	4606			agg/cct	More info
Eco147I	6	894	1017	1623	3526 3558 3806	grgcy/c	More info
Eco24I	1	6408				agt/act	More info
Eco255I	3	3380	4031	6000		ggtctc	More info
Eco31I	1	952				gat/ atc	More info
Eco32I	1	925				c/ ggccg	More info
Eco52I							

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FIG. 14-56

Eco57I	7	1210 2446 2488 3271 3314 5567 6615	ctgaag	<u>More info</u>
Eco64I	8	791 2264 3065 3434 3602 4779 5876 7036	g/ gyrcc	<u>More info</u>
Eco72I	1	2705	cac/gtg	<u>More info</u>
Eco81I	3	1034 1046 3256	cc/ tnagg	<u>More info</u>
Eco88I	3	3638 3934 4629	c/ ycgrg	<u>More info</u>
EcoICRI	1	892	gag/ ctc	<u>More info</u>
EcoNI	3	1259 1338 1684	cctnn/nnnagg	<u>More info</u>
EcoO109I	3	3291 3802 3829	rg/gnccy	<u>More info</u>
EcoRI	3	912 1990 2994	g/ aattc	<u>More info</u>
EcoRV	1	952	gat/ atc	<u>More info</u>
EcoT14I	11	686 1950 2226 3109 3324 3424 3681 4060 4178 4514 4607	c/ cwwgg	<u>More info</u>
EcoT22I	3	3961 4356 4429		
ErhI	11	686 1950 2226 3109 3324 3424 3681 4060 4178 4514 4607	atgca/t	<u>More info</u>
			c/ cwwgg	<u>More info</u>
Esp1396I	6	1445 1482 1775 1796 2644 4191	ccannnn/ntgg	<u>More info</u>
Esp3I	3	2023 2773 4001	cgtctc	<u>More info</u>
FauNDI	1	560	ca/ tatg	<u>More info</u>
FbaI	1	969	t/ gatca	<u>More info</u>
FriOI	6	894 1017 1623 3526 3558 3806	grgcy/c	<u>More info</u>
Fspi	2	21 6150	tgc/gca	<u>More info</u>

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FIG. 14-57

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GsuI	9	1015 1279 1772 2781 2842 3022	ctggag	<u>More info</u>
HaeII	5	3701 3863 6018	rgcgc/y	<u>More info</u>
HinII	6	2519 4913 5283 6922 6930	gr/cgyc	<u>More info</u>
HincII	3	448 501 584 770 4151 6465	gty/rac	<u>More info</u>
HindII	3	311 446 842	gty/rac	<u>More info</u>
HindIII	3	311 446 842	a/ agctt	<u>More info</u>
Hsp92I	6	918 1394 2183	gr/cgyc	<u>More info</u>
KpnI	3	448 501 584 770 4151 6465	ggtac/c	<u>More info</u>
Ksp22I	1	2268 3438 3606	t/ gatca	<u>More info</u>
Ksp632I	5	969	ctcttc	<u>More info</u>
LspI	3	58 2482 2793 4918 6722	tt/cgaa	<u>More info</u>
MfeI	1	1603 1988 2423	c/ aattg	<u>More info</u>
MflI	12	1091	r/ gatcy	<u>More info</u>
MluNI	4	932 2400 2634 3409 3596 3634	tgg/cca	<u>More info</u>
Mph1103I	3	5676 5687 5773 5785 6553 6570	atgca/t	<u>More info</u>
MronI	1	184 238 3300 4018	g/ ccggc	<u>More info</u>
MscI	4	3961 4356 4429	tgg/cca	<u>More info</u>
MslI	10	6972	caynn/nnrtg	<u>More info</u>
Msp17I	6	184 238 3300 4018	gr/cgyc	<u>More info</u>
MspA1I	7	691 2094 2703 3323 3489 3651	cmg/ckg	<u>More info</u>
		3698 6180 6339 6698		
		448 501 584 770 4151 6465		
		71 2341 2731 4859 5377 5622 6563		

FIG. 14-58

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MunI	1	1091		c/ aattg	More info
MvaI269I	1	1886		gaatgc	More info
NaeI	1	6974		gcc/ggc	More info
NcoI	5	686 3324 3424 4178 4514		c/ catgg	More info
NdeI	1	560		ca/ tatg	More info
NgoAIV	1	6972		g/ ccggc	More info
NgomI	1	6972		g/ ccggc	More info
NotI	1	925		gc/ggccgc	More info
NsiI	3	3961 4356 4429		atgca/t	More info
NspBII	7	71 2341 2731 4859 5377 5622 6563		cmg/ckg	More info
NspI	5	2930 3959 4354 4427 5039		rcatg/y	More info
NspV	3	1603 1988 2423		tt/cgaa	More info
PaeI	4	2930 3959 4354 4427		gcatg/c	More info
Paer7I	1	4629		c/ tcgag	More info
PflMI	6	1445 1482 1775 1796 2644 4191		ccannnn/ntgg	More info
PinAI	1	4188		a/ ccggt	More info
Ple19I	2	42 6298		cgat/cg	More info
PmaCI	1	2705		cac/gtg	More info
Pme55I	2	3446 4606		agg/cct	More info
PmlI	1	2705		cac/gtg	More info
Ppu10I	3	3957 4352 4425		a/ tgcac	More info
PshBI	4	334 4806 4865 6100		at/ taat	More info
Psp124BI	1	894		gagct/c	More info
Psp1406I	3	6154 6527 7291		aa/cgtt	More info

FIG. 14-59

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PspAI	1	3638	c/ ccggg	More info
PspALI	1	3640	ccc/ggg	More info
PspOMI	1	3802	g/ ggccc	More info
PstI	2	948 2148	ctgca/g	More info
PvuI	2	42 6298	cgat/cg	More info
PvuII	3	71 2341 4859	cag/ctg	More info
RcaI	3	1891 5755 6763	t/ catga	More info
SacI	1	894	gagct/c	More info
SapI	2	2483 4918	gctcttc	More info
ScaI	1	6408	agt/act	More info
SexAI	1	4373	a/ ccwggg	More info
SfcI	8	944 2144 3824 4662 5300 5491 6169 6854	c/ tryag	More info
SfiI	1	4560	ggccnnnn/nggcc	More info
Sfr274I	1	4629	c/ tcgag	More info
SfuI	3	1603 1988 2423	tt/cgaa	More info
SmaI	1	3640	ccc/ggg	More info
SnaBI	1	666	tac/gta	More info
SpeI	1	326	a/ ctagt	More info
SphI	4	2930 3959 4354 4427	gcatg/c	More info
SseBI	2	3446 4606	agg/cct	More info
SspBI	2	270 3471	t/ gtaca	More info
SspI	5	179 226 3768 6732 7285	aat/att	More info
SstI	1	894	gagct/c	More info

FIG. 14-60

The following endonucleases were selected but don't cut this sequence:

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FIG. 14-61

SEQUENCE LISTING

<110> Sloan-Kettering Institute for Cancer Research
Richon, Victoria
Zhou, Xianbo
Rifkind, Richard A.
Marks, Paul A.

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and Uses Thereof

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 Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
 65 70 75 80
 Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
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 Pro Thr Asn Gly Lys Asn His Ser Val Ser Arg His Pro Lys Leu Trp
 165 170 175
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 180 185 190
 Ser Gly Thr Ser Pro Ser Tyr Lys Tyr Thr Leu Pro Gly Ala Gln Asp
 195 200 205
 Ala Lys Asp Asp Phe Pro Leu Arg Lys Thr Ala Ser Glu Pro Asn Leu
 210 215 220
 Lys Val Arg Ser Arg Leu Lys Gln Lys Val Ala Glu Arg Arg Ser Ser
 225 230 235 240

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Ser	Gln	Gln	Arg	Ile	Leu	Ile	His	Glu	Asp	Ser	Met	Asn	Leu	Leu	Ser		
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Leu	Tyr	Thr	Ser	Pro	Ser	Leu	Pro	Asn	Ile	Thr	Leu	Gly	Leu	Pro	Ala		
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Cys	Glu	Thr	Gln	Thr	Leu	Arg	Gln	Gly	Val	Pro	Leu	Pro	Gly	Gln	Tyr		
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Gly	Gly	Ser	Ile	Pro	Ala	Ser	Ser	Ser	His	Pro	His	Val	Thr	Leu	Glu		
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Gly	Lys	Pro	Pro	Asn	Ser	Ser	His	Gln	Ala	Leu	Leu	Gln	His	Leu	Leu		
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50          55          60
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65          70          75          80
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 Pro Thr Asn Gly Lys Asn His Ser Val Ser Arg His Pro Lys Leu Trp
 165 170 175
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 Ser Gly Thr Ser Pro Ser Tyr Lys Tyr Thr Leu Pro Gly Ala Gln Asp
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 Ala Lys Asp Asp Phe Pro Leu Arg Lys Thr Ala Ser Glu Pro Asn Leu
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 Lys Val Arg Ser Arg Leu Lys Gln Lys Val Ala Glu Arg Arg Ser Ser
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 Ser Gln Gln Arg Ile Leu Ile His Glu Asp Ser Met Asn Leu Leu Ser
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 Leu Tyr Thr Ser Pro Ser Leu Pro Asn Ile Thr Leu Gly Leu Pro Ala
 325 330 335
 Val Pro Ser Gln Leu Asn Ala Ser Asn Ser Leu Lys Glu Lys Gln Lys
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 Cys Glu Thr Gln Thr Leu Arg Gln Gly Val Pro Leu Pro Gly Gln Tyr
 355 360 365
 Gly Gly Ser Ile Pro Ala Ser Ser Ser His Pro His Val Thr Leu Glu
 370 375 380
 Gly Lys Pro Pro Asn Ser Ser His Gln Ala Leu Leu Gln His Leu Leu
 385 390 395 400
 Leu Lys Glu Gln Met Arg Gln Gln Lys Leu Leu Val Ala Gly Gly Val
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 Pro Leu His Pro Gln Ser Pro Leu Ala Thr Lys Glu Arg Ile Ser Pro
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 Gly Ile Arg Gly Thr His Lys Leu Pro Arg His Arg Pro Leu Asn Arg
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 Thr Gln Ser Ala Pro Leu Pro Gln Ser Thr Leu Ala Gln Leu Val Ile
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 Gln Gln Gln His Gln Gln Phe Leu Glu Lys Gln Lys Gln Tyr Gln Gln
 465 470 475 480
 Gln Ile His Met Asn Lys Leu Leu Ser Lys Ser Ile Glu Gln Leu Lys
 485 490 495
 Gln Pro Gly Ser His Leu Glu Glu Ala Glu Glu Glu Leu Gln Gly Asp
 500 505 510
 Gln Ala Met Gln Glu Asp Arg Ala Pro Ser Ser Gly Asn Ser Thr Arg
 515 520 525
 Ser Asp Ser Ser Ala Cys Val Asp Asp Thr Leu Gly Gln Val Gly Ala
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 Val Lys Val Lys Glu Glu Pro Val Asp Ser Asp Glu Asp Ala Gln Ile
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 Gln Glu Met Glu Ser Gly Glu Gln Ala Ala Phe Met Gln Gln Pro Phe
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 Leu Glu Pro Thr His Thr Arg Ala Leu Ser Val Arg Gln Ala Pro Leu
 580 585 590
 Ala Ala Val Gly Met Asp Gly Leu Glu Lys His Arg Leu Val Ser Arg
 595 600 605

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Thr His Ser Ser Pro Ala Ala Ser Val Leu Pro His Pro Ala Met Asp
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 Arg Pro Leu Gln Pro Gly Ser Ala Thr Gly Ile Ala Tyr Asp Pro Leu
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 Met Leu Lys His Gln Cys Val Cys Gly Asn Ser Thr Thr His Pro Glu
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 His Ala Gly Arg Ile Gln Ser Ile Trp Ser Arg Leu Gln Glu Thr Gly
 660 665 670
 Leu Leu Asn Lys Cys Glu Arg Ile Gln Gly Arg Lys Ala Ser Leu Glu
 675 680 685
 Glu Ile Gln Leu Val His Ser Glu His His Ser Leu Leu Tyr Gly Thr
 690 695 700
 Asn Pro Leu Asp Gly Gln Lys Leu Asp Pro Arg Ile Leu Leu Gly Asp
 705 710 715 720
 Asp Ser Gln Lys Phe Phe Ser Ser Leu Pro Cys Gly Gly Leu Gly Val
 725 730 735
 Asp Ser Asp Thr Ile Trp Asn Glu Leu His Ser Ser Gly Ala Ala Arg
 740 745 750
 Met Ala Val Gly Cys Val Ile Glu Leu Ala Ser Lys Val Ala Ser Gly
 755 760 765
 Glu Leu Lys Asn Gly Phe Ala Val Val Arg Pro Pro Gly His His Ala
 770 775 780
 Glu Glu Ser Thr Ala Met Gly Phe Cys Phe Phe Asn Ser Val Ala Ile
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 Thr Ala Lys Tyr Leu Arg Asp Gln Leu Asn Ile Ser Lys Ile Leu Ile
 805 810 815
 Val Asp Leu Asp Val His His Gly Asn Gly Thr Gln Gln Ala Phe Tyr
 820 825 830
 Ala Asp Pro Ser Ile Leu Tyr Ile Ser Leu His Arg Tyr Asp Glu Gly
 835 840 845
 Asn Phe Phe Pro Gly Ser Gly Ala Pro Asn Glu Val Arg Phe Ile Ser
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<211> 3054

<212> DNA

<213> Homo sapiens

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<210> 6

<211> 967

<212> PRT

<213> Homo sapiens

<400> 6

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Met Met Pro Val Val Asp Pro Val Val Arg Glu Lys Gln Leu Gln Gln
35      40      45
Glu Leu Leu Leu Ile Gln Gln Gln Gln Gln Ile Gln Lys Gln Leu Leu
50      55      60
Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
65      70      75      80
Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
85      90      95
Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
100     105     110
Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
115     120     125
Gly Lys Asp Arg Gly Arg Glu Arg Ala Val Ala Ser Thr Glu Val Lys
130     135     140
Gln Lys Leu Gln Glu Phe Leu Leu Ser Lys Ser Ala Thr Lys Asp Thr
145     150     155     160
Pro Thr Asn Gly Lys Asn His Ser Val Ser Arg His Pro Lys Leu Trp
165     170     175
Tyr Thr Ala Ala His His Thr Ser Leu Asp Gln Ser Ser Pro Pro Leu
180     185     190

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Asn	Leu	Leu	Ser	Leu	Tyr	Thr	Ser	Pro	Ser	Leu	Pro	Asn	Ile	Thr	Leu		
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Gly	Leu	Pro	Ala	Val	Pro	Ser	Gln	Leu	Asn	Ala	Ser	Asn	Ser	Leu	Lys		
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Glu	Lys	Gln	Lys	Cys	Glu	Thr	Gln	Thr	Leu	Arg	Gln	Gly	Val	Pro	Leu		
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Pro	Gly	Gln	Tyr	Gly	Gly	Ser	Ile	Pro	Ala	Ser	Ser	Ser	His	Pro	His		
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Val	Thr	Leu	Glu	Gly	Lys	Pro	Pro	Asn	Ser	Ser	His	Gln	Ala	Leu	Leu		
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Gln	His	Leu	Leu	Leu	Lys	Glu	Gln	Met	Arg	Gln	Gln	Lys	Leu	Leu	Val		
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Ala	Gly	Gly	Val	Pro	Leu	His	Pro	Gln	Ser	Pro	Leu	Ala	Thr	Lys	Glu		
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Arg	Ile	Ser	Pro	Gly	Ile	Arg	Gly	Thr	His	Lys	Leu	Pro	Arg	His	Arg		
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Pro	Leu	Asn	Arg	Thr	Gln	Ser	Ala	Pro	Leu	Pro	Gln	Ser	Thr	Leu	Ala		
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Gln	Leu	Val	Ile	Gln	Gln	Gln	His	Gln	Gln	Phe	Leu	Glu	Lys	Gln	Lys		
			420					425					430				
Gln	Tyr	Gln	Gln	Gln	Ile	His	Met	Asn	Lys	Leu	Leu	Ser	Lys	Ser	Ile		
		435					440					445					
Glu	Gln	Leu	Lys	Gln	Pro	Gly	Ser	His	Leu	Glu	Glu	Ala	Glu	Glu	Glu		
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Leu	Gln	Gly	Asp	Gln	Ala	Met	Gln	Glu	Asp	Arg	Ala	Pro	Ser	Ser	Gly		
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				485					490					495			
Gln	Val	Gly	Ala	Val	Lys	Val	Lys	Glu	Glu	Pro	Val	Asp	Ser	Asp	Glu		
			500					505					510				
Asp	Ala	Gln	Ile	Gln	Glu	Met	Glu	Ser	Gly	Glu	Gln	Ala	Ala	Phe	Met		
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Gln	Gln	Pro	Phe	Leu	Glu	Pro	Thr	His	Thr	Arg	Ala	Leu	Ser	Val	Arg		
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Gln	Ala	Pro	Leu	Ala	Ala	Val	Gly	Met	Asp	Gly	Leu	Glu	Lys	His	Arg		
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Pro	Ala	Met	Asp	Arg	Pro	Leu	Gln	Pro	Gly	Ser	Ala	Thr	Gly	Ile	Ala		
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Tyr	Asp	Pro	Leu	Met	Leu	Lys	His	Gln	Cys	Val	Cys	Gly	Asn	Ser	Thr		
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Thr	His	Pro	Glu	His	Ala	Gly	Arg	Ile	Gln	Ser	Ile	Trp	Ser	Arg	Leu		
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Gln	Glu	Thr	Gly	Leu	Leu	Asn	Lys	Cys	Glu	Arg	Ile	Gln	Gly	Arg	Lys		
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Ala	Ser	Leu	Glu	Glu	Ile	Gln	Leu	Val	His	Ser	Glu	His	His	Ser	Leu		
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Leu	Tyr	Gly	Thr	Asn	Pro	Leu	Asp	Gly	Gln	Lys	Leu	Asp	Pro	Arg	Ile		
			660					665					670				
Leu	Leu	Gly	Asp	Asp	Ser	Gln	Lys	Phe	Phe	Ser	Ser	Leu	Pro	Cys	Gly		
		675					680						685				

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 Gly Ala Ala Arg Met Ala Val Gly Cys Val Ile Glu Leu Ala Ser Lys
 705 710 715 720
 Val Ala Ser Gly Glu Leu Lys Asn Gly Phe Ala Val Val Arg Pro Pro
 725 730 735
 Gly His His Ala Glu Glu Ser Thr Ala Met Gly Phe Cys Phe Phe Asn
 740 745 750
 Ser Val Ala Ile Thr Ala Lys Tyr Leu Arg Asp Gln Leu Asn Ile Ser
 755 760 765
 Lys Ile Leu Ile Val Asp Leu Asp Val His His Gly Asn Gly Thr Gln
 770 775 780
 Gln Ala Phe Tyr Ala Asp Pro Ser Ile Leu Tyr Ile Ser Leu His Arg
 785 790 795 800
 Tyr Asp Glu Gly Asn Phe Phe Pro Gly Ser Gly Ala Pro Asn Glu Val
 805 810 815
 Gly Thr Gly Leu Gly Glu Gly Tyr Asn Ile Asn Ile Ala Trp Thr Gly
 820 825 830
 Gly Leu Asp Pro Pro Met Gly Asp Val Glu Tyr Leu Glu Ala Phe Arg
 835 840 845
 Thr Ile Val Lys Pro Val Ala Lys Glu Phe Asp Pro Asp Met Val Leu
 850 855 860
 Val Ser Ala Gly Phe Asp Ala Leu Glu Gly His Thr Pro Pro Leu Gly
 865 870 875 880
 Gly Tyr Lys Val Thr Ala Lys Cys Phe Gly His Leu Thr Lys Gln Leu
 885 890 895
 Met Thr Leu Ala Asp Gly Arg Val Val Leu Ala Leu Glu Gly Gly His
 900 905 910
 Asp Leu Thr Ala Ile Cys Asp Ala Ser Glu Ala Cys Val Asn Ala Leu
 915 920 925
 Leu Gly Asn Glu Leu Glu Pro Leu Ala Glu Asp Ile Leu His Gln Ser
 930 935 940
 Pro Asn Met Asn Ala Val Ile Ser Leu Gln Lys Ile Ile Glu Ile Gln
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 Ser Met Ser Leu Lys Phe Ser
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<210> 7

<211> 3367

<212> DNA

<213> Homo sapiens

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<210> 8

<211> 835

<212> PRT

<213> Homo sapiens

<400> 8

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35          40          45
Glu Leu Leu Leu Ile Gln Gln Gln Gln Gln Ile Gln Lys Gln Leu Leu
50          55          60
Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
65          70          75          80
Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
85          90          95
Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
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Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
115         120         125

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Pro	Thr	Asn	Gly	Lys	Asn	His	Ser	Val	Ser	Arg	His	Pro	Lys	Leu	Trp
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Tyr	Thr	Ala	Ala	His	His	Thr	Ser	Leu	Asp	Gln	Ser	Ser	Pro	Pro	Leu
				180					185				190		
Ser	Gly	Thr	Ser	Pro	Ser	Tyr	Lys	Tyr	Thr	Leu	Pro	Gly	Ala	Gln	Asp
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Ala	Lys	Asp	Asp	Phe	Pro	Leu	Arg	Lys	Thr	Glu	Ser	Ser	Val	Ser	Ser
		210				215					220				
Ser	Ser	Pro	Gly	Ser	Gly	Pro	Ser	Ser	Pro	Asn	Asn	Gly	Pro	Thr	Gly
225					230					235					240
Ser	Val	Thr	Glu	Asn	Glu	Thr	Ser	Val	Leu	Pro	Pro	Thr	Pro	His	Ala
				245					250					255	
Glu	Gln	Met	Val	Ser	Gln	Gln	Arg	Ile	Leu	Ile	His	Glu	Asp	Ser	Met
			260					265					270		
Asn	Leu	Leu	Ser	Leu	Tyr	Thr	Ser	Pro	Ser	Leu	Pro	Asn	Ile	Thr	Leu
		275					280					285			
Gly	Leu	Pro	Ala	Val	Pro	Ser	Gln	Leu	Asn	Ala	Ser	Asn	Ser	Leu	Lys
		290				295					300				
Glu	Lys	Gln	Lys	Cys	Glu	Thr	Gln	Thr	Leu	Arg	Gln	Gly	Val	Pro	Leu
305					310					315					320
Pro	Gly	Gln	Tyr	Gly	Gly	Ser	Ile	Pro	Ala	Ser	Ser	Ser	His	Pro	His
				325					330					335	
Val	Thr	Leu	Glu	Gly	Lys	Pro	Pro	Asn	Ser	Ser	His	Gln	Ala	Leu	Leu
			340					345					350		
Gln	His	Leu	Leu	Leu	Lys	Glu	Gln	Met	Arg	Gln	Gln	Lys	Leu	Leu	Val
		355					360					365			
Ala	Gly	Gly	Val	Pro	Leu	His	Pro	Gln	Ser	Pro	Leu	Ala	Thr	Lys	Glu
		370				375					380				
Arg	Ile	Ser	Pro	Gly	Ile	Arg	Gly	Thr	His	Lys	Leu	Pro	Arg	His	Arg
385					390					395					400
Pro	Leu	Asn	Arg	Thr	Gln	Ser	Ala	Pro	Leu	Pro	Gln	Ser	Thr	Leu	Ala
				405					410					415	
Gln	Leu	Val	Ile	Gln	Gln	Gln	His	Gln	Gln	Phe	Leu	Glu	Lys	Gln	Lys
			420					425					430		
Gln	Tyr	Gln	Gln	Gln	Ile	His	Met	Asn	Lys	Leu	Leu	Ser	Lys	Ser	Ile
		435					440					445			
Glu	Gln	Leu	Lys	Gln	Pro	Gly	Ser	His	Leu	Glu	Glu	Ala	Glu	Glu	Glu
		450				455					460				
Leu	Gln	Gly	Asp	Gln	Ala	Met	Gln	Glu	Asp	Arg	Ala	Pro	Ser	Ser	Gly
465					470					475					480
Asn	Ser	Thr	Arg	Ser	Asp	Ser	Ser	Ala	Cys	Val	Asp	Asp	Thr	Leu	Gly
				485					490					495	
Gln	Val	Gly	Ala	Val	Lys	Val	Lys	Glu	Glu	Pro	Val	Asp	Ser	Asp	Glu
			500					505					510		
Asp	Ala	Gln	Ile	Gln	Glu	Met	Glu	Ser	Gly	Glu	Gln	Ala	Ala	Phe	Met
		515					520					525			
Gln	Gln	Pro	Phe	Leu	Glu	Pro	Thr	His	Thr	Arg	Ala	Leu	Ser	Val	Arg
		530					535				540				
Gln	Ala	Pro	Leu	Ala	Ala	Val	Gly	Met	Asp	Gly	Leu	Glu	Lys	His	Arg
545					550					555					560
Leu	Val	Ser	Arg	Thr	His	Ser	Ser	Pro	Ala	Ala	Ser	Val	Leu	Pro	His
				565					570					575	
Pro	Ala	Met	Asp	Arg	Pro	Leu	Gln	Pro	Gly	Ser	Ala	Thr	Gly	Ile	Ala
			580					585					590		
Tyr	Asp	Pro	Leu	Met	Leu	Lys	His	Gln	Cys	Val	Cys	Gly	Asn	Ser	Thr
		595					600					605			
Thr	His	Pro	Glu	His	Ala	Gly	Arg	Ile	Gln	Ser	Ile	Trp	Ser	Arg	Leu
		610				615					620				

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Gln Glu Thr Gly Leu Leu Asn Lys Cys Glu Arg Ile Gln Gly Arg Lys
 625 630 635 640
 Ala Ser Leu Glu Glu Ile Gln Leu Val His Ser Glu His His Ser Leu
 645 650 655
 Leu Tyr Gly Thr Asn Pro Leu Asp Gly Gln Lys Leu Asp Pro Arg Ile
 660 665 670
 Leu Leu Gly Asp Asp Ser Gln Lys Phe Phe Ser Ser Leu Pro Cys Gly
 675 680 685
 Gly Leu Gly Val Asp Ser Asp Thr Ile Trp Asn Glu Leu His Ser Ser
 690 695 700
 Gly Ala Ala Arg Met Ala Val Gly Cys Val Ile Glu Leu Ala Ser Lys
 705 710 715 720
 Val Ala Ser Gly Glu Leu Lys Asn Gly Phe Ala Val Val Arg Pro Pro
 725 730 735
 Gly His His Ala Glu Glu Ser Thr Ala Met Gly Phe Cys Phe Phe Asn
 740 745 750
 Ser Val Ala Ile Thr Ala Lys Tyr Leu Arg Asp Gln Leu Asn Ile Ser
 755 760 765
 Lys Ile Leu Ile Val Asp Leu Asp Val His His Gly Asn Gly Thr Gln
 770 775 780
 Gln Ala Phe Tyr Ala Asp Pro Ser Ile Leu Tyr Ile Ser Leu His Arg
 785 790 795 800
 Tyr Asp Glu Gly Asn Phe Phe Pro Gly Ser Gly Ala Pro Asn Glu Val
 805 810 815
 Arg Phe Ile Ser Leu Glu Pro His Phe Tyr Leu Tyr Leu Ser Gly Asn
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 Cys Ile Ala
 835

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 <211> 1791
 <212> DNA
 <213> Homo sapiens

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 ggacgagagc agctcttggc tcagcaaaga atgcacagta tgatcagctc agtggatgtg 180
 aagtcagaag ttctgttggg cctggagccc atctcacctt tagacctaa gacagacctc 240
 aggatgatga tgcccggtgt ggaccctgtt gtccgtgaga agcaattgca gcaggaatta 300
 ctcttatccc agcagcagca acaaatccag aagcagcttc tgatagcaga gtttcagaaa 360
 cagcatgaga acttgacacg gcagcaccag gctcagcttc aggagcatat caaggaactt 420
 ctagccataa aacagcaaca agaactccta gaaaaggagc agaaactgga gcagcagagg 480
 caagaacagg aagtagagag gcatcgaga gaacagcagc ttcctcctct cagaggcaaa 540
 gatagaggac gagaaagggc agtggcaagt acagaagtaa agcagaagct tcaagagttc 600
 ctactgagta aatcagcaac gaaagacact ccaactaatg gaaaaaatca ttccgtgagc 660
 cgccatccca agctctgtga cagggtgcc caccacacat cattggatca aagctctcca 720
 ccccttagtg gaacatctcc atctacaag tacacattac caggagcaca agatgcaaag 780
 gatgatttcc cccttcgaaa aactgaatcc tcagtcagta gcagttctcc aggtctgtgt 840
 cccagttcac caaacaatgg gccaactgga agtggtactg aaaatgagac ttcgggtttt 900
 cccctaccc ctcatgccga gcaaatggtt tcacagcaac gcattctaatt tcatgaagat 960
 tccatgaacc tgctaagtct ttatacctct ccttctttgc ccaacattac cttggggctt 1020
 cccgcagtgc catcccagct caatgcttcg aattcactca aagaaaagca gaagtgtgag 1080
 acgcagacgc ttaggcaagg tgttcctctg cctgggcagt atggaggcag catcccgga 1140
 tcttcagcc accctcatgt tactttagag ggaaagccac ccaacagcag ccaccaggct 1200
 ctctgcagc atttattatt gaaagaacaa atgcgacagc aaaagcttct ttagctgtgt 1260
 ggagttccct tacatcctca gtctcccttg gcaacaaaag agagaatttc acctggcatt 1320
 agaggtaccc acaaattgcc ccgtcacaga cccctgaacc gaaccagtc tgcacctttg 1380
 cctcagagca cgttgggtca gctgggtcatt caacagcaac accagcaatt cttggagaag 1440
 cagaagcaat accagcagca gatccacatg aacaaactgc tttcgaaatc tattgaacaa 1500
 ctgaagcaac caggcagtc ccttgaggaa gcagaggaag agcttcaggg ggaccaggcg 1560

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atgcaggaag acagagcgcc ctctagtggc aacagcacta ggagcgacag cagtgtttgt 1620
gtgggatgaca cactggggaca agttggggct gtgaagggtca aggaggaacc agtggacagt 1680
gatgaagatg ctcagatcca ggaaatggaa tctgggggagc aggctgcttt tatgcaacag 1740
gtaataggca aagatttagc tccaggattt gtaattaaag tcattatctg a 1791

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<210> 10

<211> 546

<212> PRT

<213> Homo sapiens

<400> 10

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 20      25      30
Met Met Pro Val Val Asp Pro Val Val Arg Glu Lys Gln Leu Gln Gln
 35      40      45
Glu Leu Leu Leu Ile Gln Gln Gln Gln Ile Gln Lys Gln Leu Leu
 50      55      60
Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
 65      70      75      80
Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
 85      90      95
Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
100      105      110
Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
115      120      125
Gly Lys Asp Arg Gly Arg Glu Arg Ala Val Ala Ser Thr Glu Val Lys
130      135      140
Gln Lys Leu Gln Glu Phe Leu Leu Ser Lys Ser Ala Thr Lys Asp Thr
145      150      155      160
Pro Thr Asn Gly Lys Asn His Ser Val Ser Arg His Pro Lys Leu Trp
165      170      175
Tyr Thr Ala Ala His His Thr Ser Leu Asp Gln Ser Ser Pro Pro Leu
180      185      190
Ser Gly Thr Ser Pro Ser Tyr Lys Tyr Thr Leu Pro Gly Ala Gln Asp
195      200      205
Ala Lys Asp Asp Phe Pro Leu Arg Lys Thr Glu Ser Ser Val Ser Ser
210      215      220
Ser Ser Pro Gly Ser Gly Pro Ser Ser Pro Asn Asn Gly Pro Thr Gly
225      230      235      240
Ser Val Thr Glu Asn Glu Thr Ser Val Leu Pro Pro Thr Pro His Ala
245      250      255
Glu Gln Met Val Ser Gln Gln Arg Ile Leu Ile His Glu Asp Ser Met
260      265      270
Asn Leu Leu Ser Leu Tyr Thr Ser Pro Ser Leu Pro Asn Ile Thr Leu
275      280      285
Gly Leu Pro Ala Val Pro Ser Gln Leu Asn Ala Ser Asn Ser Leu Lys
290      295      300
Glu Lys Gln Lys Cys Glu Thr Gln Thr Leu Arg Gln Gly Val Pro Leu
305      310      315      320
Pro Gly Gln Tyr Gly Gly Ser Ile Pro Ala Ser Ser Ser His Pro His
325      330      335
Val Thr Leu Glu Gly Lys Pro Pro Asn Ser Ser His Gln Ala Leu Leu
340      345      350
Gln His Leu Leu Leu Lys Glu Gln Met Arg Gln Gln Lys Leu Leu Val
355      360      365
Ala Gly Gly Val Pro Leu His Pro Gln Ser Pro Leu Ala Thr Lys Glu
370      375      380
Arg Ile Ser Pro Gly Ile Arg Gly Thr His Lys Leu Pro Arg His Arg
385      390      395      400
Pro Leu Asn Arg Thr Gln Ser Ala Pro Leu Pro Gln Ser Thr Leu Ala

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405 410 415
 Gln Leu Val Ile Gln Gln Gln His Gln Gln Phe Leu Glu Lys Gln Lys
 420 425 430
 Gln Tyr Gln Gln Gln Ile His Met Asn Lys Leu Leu Ser Lys Ser Ile
 435 440 445
 Glu Gln Leu Lys Gln Pro Gly Ser His Leu Glu Glu Ala Glu Glu Glu
 450 455 460
 Leu Gln Gly Asp Gln Ala Met Gln Glu Asp Arg Ala Pro Ser Ser Gly
 465 470 475 480
 Asn Ser Thr Arg Ser Asp Ser Ser Ala Cys Val Asp Asp Thr Leu Gly
 485 490 495
 Gln Val Gly Ala Val Lys Val Lys Glu Glu Pro Val Asp Ser Asp Glu
 500 505 510
 Asp Ala Gln Ile Gln Glu Met Glu Ser Gly Glu Gln Ala Ala Phe Met
 515 520 525
 Gln Gln Val Ile Gly Lys Asp Leu Ala Pro Gly Phe Val Ile Lys Val
 530 535 540
 Ile Ile
 545

<210> 11
 <211> 590
 <212> PRT
 <213> Homo sapiens

<400> 11
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 Gly Leu Glu Pro Ile Ser Pro Leu Asp Leu Arg Thr Asp Leu Arg Met
 20 25 30
 Met Met Pro Val Val Asp Pro Val Arg Glu Lys Gln Leu Gln Gln
 35 40 45
 Glu Leu Leu Leu Ile Gln Gln Gln Gln Gln Ile Gln Lys Gln Leu Leu
 50 55 60
 Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
 65 70 75 80
 Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
 85 90 95
 Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
 100 105 110
 Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
 115 120 125
 Gly Lys Asp Arg Gly Arg Glu Arg Ala Val Ala Ser Thr Glu Val Lys
 130 135 140
 Gln Lys Leu Gln Glu Phe Leu Leu Ser Lys Ser Ala Thr Lys Asp Thr
 145 150 155 160
 Pro Thr Asn Gly Lys Asn His Ser Val Ser Arg His Pro Lys Leu Trp
 165 170 175
 Tyr Thr Ala Ala His His Thr Ser Leu Asp Gln Ser Ser Pro Pro Leu
 180 185 190
 Ser Gly Thr Ser Pro Ser Tyr Lys Tyr Thr Leu Pro Gly Ala Gln Asp
 195 200 205
 Ala Lys Asp Asp Phe Pro Leu Arg Lys Thr Ala Ser Glu Pro Asn Leu
 210 215 220
 Lys Val Arg Ser Arg Leu Lys Gln Lys Val Ala Glu Arg Arg Ser Ser
 225 230 235 240
 Pro Leu Leu Arg Arg Lys Asp Gly Asn Val Val Thr Ser Phe Lys Lys
 245 250 255
 Arg Met Phe Glu Val Thr Glu Ser Ser Val Ser Ser Ser Ser Pro Gly
 260 265 270
 Ser Gly Pro Ser Ser Pro Asn Asn Gly Pro Thr Gly Ser Val Thr Glu

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      275              280              285
Asn Glu Thr Ser Val Leu Pro Pro Thr Pro His Ala Glu Gln Met Val
290              295              300
Ser Gln Gln Arg Ile Leu Ile His Glu Asp Ser Met Asn Leu Leu Ser
305              310              315
Leu Tyr Thr Ser Pro Ser Leu Pro Asn Ile Thr Leu Gly Leu Pro Ala
      325              330              335
Val Pro Ser Gln Leu Asn Ala Ser Asn Ser Leu Lys Glu Lys Gln Lys
      340              345              350
Cys Glu Thr Gln Thr Leu Arg Gln Gly Val Pro Leu Pro Gly Gln Tyr
      355              360              365
Gly Gly Ser Ile Pro Ala Ser Ser Ser His Pro His Val Thr Leu Glu
370              375              380
Gly Lys Pro Pro Asn Ser Ser His Gln Ala Leu Leu Gln His Leu Leu
385              390              395
Leu Lys Glu Gln Met Arg Gln Gln Lys Leu Leu Val Ala Gly Gly Val
      405              410              415
Pro Leu His Pro Gln Ser Pro Leu Ala Thr Lys Glu Arg Ile Ser Pro
      420              425              430
Gly Ile Arg Gly Thr His Lys Leu Pro Arg His Arg Pro Leu Asn Arg
      435              440              445
Thr Gln Ser Ala Pro Leu Pro Gln Ser Thr Leu Ala Gln Leu Val Ile
450              455              460
Gln Gln Gln His Gln Gln Phe Leu Glu Lys Gln Lys Gln Tyr Gln Gln
465              470              475
Gln Ile His Met Asn Lys Leu Leu Ser Lys Ser Ile Glu Gln Leu Lys
      485              490              495
Gln Pro Gly Ser His Leu Glu Glu Ala Glu Glu Glu Leu Gln Gly Asp
500              505              510
Gln Ala Met Gln Glu Asp Arg Ala Pro Ser Ser Gly Asn Ser Thr Arg
      515              520              525
Ser Asp Ser Ser Ala Cys Val Asp Asp Thr Leu Gly Gln Val Gly Ala
530              535              540
Val Lys Val Lys Glu Glu Pro Val Asp Ser Asp Glu Asp Ala Gln Ile
545              550              555
Gln Glu Met Glu Ser Gly Glu Gln Ala Ala Phe Met Gln Gln Val Ile
      565              570              575
Gly Lys Asp Leu Ala Pro Gly Phe Val Ile Lys Val Ile Ile
580              585              590

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<210> 12

<211> 1084

<212> PRT

<213> Homo sapiens

<400> 12

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Met Ser Ser Gln Ser His Pro Asp Gly Leu Ser Gly Arg Asp Gln Pro
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Val Glu Leu Leu Asn Pro Ala Arg Val Asn His Met Pro Ser Thr Val
      20              25              30
Asp Val Ala Thr Ala Leu Pro Leu Gln Val Ala Pro Ser Ala Val Pro
      35              40              45
Met Asp Leu Arg Leu Asp His Gln Phe Ser Leu Pro Val Ala Glu Pro
50              55              60
Ala Leu Arg Glu Gln Gln Leu Gln Gln Glu Leu Leu Ala Leu Lys Gln
65              70              75              80
Lys Gln Gln Ile Gln Arg Gln Ile Leu Ile Ala Glu Phe Gln Arg Gln
      85              90              95
His Glu Gln Leu Ser Arg Gln His Glu Ala Gln Leu His Glu His Ile
      100              105              110
Lys Gln Gln Gln Glu Met Leu Ala Met Lys His Gln Gln Glu Leu Leu

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610	615	620
Arg Pro Leu Ser Arg Ala Gln Ser Ser Pro Ala Ser Ala Thr Phe Pro		
625	630	635
Val Ser Val Gln Glu Pro Pro Thr Lys Pro Arg Phe Thr Thr Gly Leu		
	645	650
Val Tyr Asp Thr Leu Met Leu Lys His Gln Cys Thr Cys Gly Ser Ser		
	660	665
Ser Ser His Pro Glu His Ala Gly Arg Ile Gln Ser Ile Trp Ser Arg		
	675	680
Leu Gln Glu Thr Gly Leu Arg Gly Lys Cys Glu Cys Ile Arg Gly Arg		
	690	700
Lys Ala Thr Leu Glu Glu Leu Gln Thr Val His Ser Glu Ala His Thr		
705	710	715
Leu Leu Tyr Gly Thr Asn Pro Leu Asn Arg Gln Lys Leu Asp Ser Lys		
	725	730
Lys Leu Leu Gly Ser Leu Ala Ser Val Phe Val Arg Leu Pro Cys Gly		
	740	745
Gly Val Gly Val Asp Ser Asp Thr Ile Trp Asn Glu Val His Ser Ala		
	755	760
Gly Ala Ala Arg Leu Ala Val Gly Cys Val Val Glu Leu Val Phe Lys		
	770	775
Val Ala Thr Gly Glu Leu Lys Asn Gly Phe Ala Val Val Arg Pro Pro		
785	790	795
Gly His His Ala Glu Ser Thr Pro Met Gly Phe Cys Tyr Phe Asn		
	805	810
Ser Val Ala Val Ala Ala Lys Leu Leu Gln Gln Arg Leu Ser Val Ser		
	820	825
Lys Ile Leu Ile Val Asp Trp Asp Val His His Gly Asn Gly Thr Gln		
	835	840
Gln Ala Phe Tyr Ser Asp Pro Ser Val Leu Tyr Met Ser Leu His Arg		
	850	855
Tyr Asp Asp Gly Asn Phe Phe Pro Gly Ser Gly Ala Pro Asp Glu Val		
865	870	875
Gly Thr Gly Pro Gly Val Gly Phe Asn Val Asn Met Ala Phe Thr Gly		
	885	890
Gly Leu Asp Pro Pro Met Gly Asp Ala Glu Tyr Leu Ala Ala Phe Arg		
	900	905
Thr Val Val Met Pro Ile Ala Ser Glu Phe Ala Pro Asp Val Val Leu		
	915	920
Val Ser Ser Gly Phe Asp Ala Val Glu Gly His Pro Thr Pro Leu Gly		
	930	935
Gly Tyr Asn Leu Ser Ala Arg Cys Phe Gly Tyr Leu Thr Lys Gln Leu		
945	950	955
Met Gly Leu Ala Gly Arg Ile Val Leu Ala Leu Glu Gly Gly His		
	965	970
Asp Leu Thr Ala Ile Cys Asp Ala Ser Glu Ala Cys Val Ser Ala Leu		
	980	985
Leu Gly Asn Glu Leu Asp Pro Leu Pro Glu Lys Val Leu Gln Gln Arg		
	995	1000
Pro Asn Ala Asn Ala Val Arg Ser Met Glu Lys Val Met Glu Ile His		
	1010	1015
Ser Lys Tyr Trp Arg Cys Leu Gln Arg Thr Thr Ser Thr Ala Gly Arg		
1025	1030	1035
Ser Leu Ile Glu Ala Thr Cys Glu Asn Glu Glu Ala Glu Thr Val		
	1045	1050
Thr Ala Met Ala Ser Leu Ser Val Gly Val Lys Pro Ala Glu Lys Arg		
	1060	1065
Pro Asp Glu Glu Pro Met Glu Glu Glu Pro Pro Leu		
	1075	1080

<210> 13

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<211> 3550

<212> DNA

<213> Homo sapiens

<400> 13

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ctagccataa	aacagcaaca	agaactccta	gaaaaggagc	agaaactgga	gcagcagagg	480
caagaacagg	aagtagagag	gcacgcgaga	gaacagcagc	ttcctcctct	cagaggcaaa	540
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25/25

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<212> PRT

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 50          55          60
Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
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Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
 85          90          95
Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
100          105          110
Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
115          120          125
Gly Lys Asp Arg Gly Arg Glu Arg Ala Val Ala Ser Thr Glu Val Lys
130          135          140
Gln Lys Leu Gln Glu Phe Leu Leu Ser Lys Ser Ala Thr Lys Asp Thr
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Tyr Thr Ala Ala His His Thr Ser Leu Asp Gln Ser Ser Pro Pro Leu
180          185          190

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 675 680 685

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ccaccgtggt gtgcttttct ctcccaggc ttggaacaggc cttggagaag ggtacaatat 2940
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attcaggacc atcgtgaagc ctgtggccaa agagtttgat ccagacatgg tcttagtata 3060
tgctggattt gatgcattgg aaggccacac ccctcctcta ggaggggtaca aagtgacggc 3120
aaaatgtttt ggtcatttga cgaagcaatt gatgacattg gctgatggac gtgtgggtgt 3180
ggctctagaa ggaggacatg atctcacagc catctgtgat gcatcagaag cctgtgtaaa 3240
tgcccttcta ggaaatgagc tggagccact tgcagaagat attctccacc aaagccccga 3300
tatgaatgct gttatttctt tacagaagat cattgaaatt caaagtatgt ctttaaagtt 3360
ctcttaa
3367

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<210> 8

<211> 835

<212> PRT

<213> Homo sapiens

<400> 8

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Met His Ser Met Ile Ser Ser Val Asp Val Lys Ser Glu Val Pro Val
1      5      10      15
Gly Leu Glu Pro Ile Ser Pro Leu Asp Leu Arg Thr Asp Leu Arg Met
20      25      30
Met Met Pro Val Val Asp Pro Val Val Arg Glu Lys Gln Leu Gln Gln
35      40      45
Glu Leu Leu Leu Ile Gln Gln Gln Gln Ile Gln Lys Gln Leu Leu
50      55      60
Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
65      70      75      80
Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
85      90      95
Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
100     105     110
Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
115     120     125

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Gly	Lys	Asp	Arg	Gly	Arg	Glu	Arg	Ala	Val	Ala	Ser	Thr	Glu	Val	Lys
130						135					140				
Gln	Lys	Leu	Gln	Glu	Phe	Leu	Leu	Ser	Lys	Ser	Ala	Thr	Lys	Asp	Thr
145					150					155					160
Pro	Thr	Asn	Gly	Lys	Asn	His	Ser	Val	Ser	Arg	His	Pro	Lys	Leu	Trp
				165					170					175	
Tyr	Thr	Ala	Ala	His	His	Thr	Ser	Leu	Asp	Gln	Ser	Ser	Pro	Pro	Leu
				180				185					190		
Ser	Gly	Thr	Ser	Pro	Ser	Tyr	Lys	Tyr	Thr	Leu	Pro	Gly	Ala	Gln	Asp
				195			200					205			
Ala	Lys	Asp	Asp	Phe	Pro	Leu	Arg	Lys	Thr	Glu	Ser	Ser	Val	Ser	Ser
						215					220				
Ser	Ser	Pro	Gly	Ser	Gly	Pro	Ser	Ser	Pro	Asn	Asn	Gly	Pro	Thr	Gly
225					230					235					240
Ser	Val	Thr	Glu	Asn	Glu	Thr	Ser	Val	Leu	Pro	Pro	Thr	Pro	His	Ala
				245					250					255	
Glu	Gln	Met	Val	Ser	Gln	Gln	Arg	Ile	Leu	Ile	His	Glu	Asp	Ser	Met
			260					265					270		
Asn	Leu	Leu	Ser	Leu	Tyr	Thr	Ser	Pro	Ser	Leu	Pro	Asn	Ile	Thr	Leu
				275			280					285			
Gly	Leu	Pro	Ala	Val	Pro	Ser	Gln	Leu	Asn	Ala	Ser	Asn	Ser	Leu	Lys
						295					300				
Glu	Lys	Gln	Lys	Cys	Glu	Thr	Gln	Thr	Leu	Arg	Gln	Gly	Val	Pro	Leu
305					310					315					320
Pro	Gly	Gln	Tyr	Gly	Gly	Ser	Ile	Pro	Ala	Ser	Ser	Ser	His	Pro	His
				325					330					335	
Val	Thr	Leu	Glu	Gly	Lys	Pro	Pro	Asn	Ser	Ser	His	Gln	Ala	Leu	Leu
				340				345					350		
Gln	His	Leu	Leu	Leu	Lys	Glu	Gln	Met	Arg	Gln	Gln	Lys	Leu	Leu	Val
				355			360					365			
Ala	Gly	Gly	Val	Pro	Leu	His	Pro	Gln	Ser	Pro	Leu	Ala	Thr	Lys	Glu
						375					380				
Arg	Ile	Ser	Pro	Gly	Ile	Arg	Gly	Thr	His	Lys	Leu	Pro	Arg	His	Arg
385					390					395					400
Pro	Leu	Asn	Arg	Thr	Gln	Ser	Ala	Pro	Leu	Pro	Gln	Ser	Thr	Leu	Ala
				405					410					415	
Gln	Leu	Val	Ile	Gln	Gln	Gln	His	Gln	Gln	Phe	Leu	Glu	Lys	Gln	Lys
				420				425					430		
Gln	Tyr	Gln	Gln	Gln	Ile	His	Met	Asn	Lys	Leu	Leu	Ser	Lys	Ser	Ile
				435			440					445			
Glu	Gln	Leu	Lys	Gln	Pro	Gly	Ser	His	Leu	Glu	Glu	Ala	Glu	Glu	Glu
				450		455					460				
Leu	Gln	Gly	Asp	Gln	Ala	Met	Gln	Glu	Asp	Arg	Ala	Pro	Ser	Ser	Gly
465					470					475					480
Asn	Ser	Thr	Arg	Ser	Asp	Ser	Ser	Ala	Cys	Val	Asp	Asp	Thr	Leu	Gly
				485					490					495	
Gln	Val	Gly	Ala	Val	Lys	Val	Lys	Glu	Glu	Pro	Val	Asp	Ser	Asp	Glu
				500				505					510		
Asp	Ala	Gln	Ile	Gln	Glu	Met	Glu	Ser	Gly	Glu	Gln	Ala	Ala	Phe	Met
				515			520					525			
Gln	Gln	Pro	Phe	Leu	Glu	Pro	Thr	His	Thr	Arg	Ala	Leu	Ser	Val	Arg
						535					540				
Gln	Ala	Pro	Leu	Ala	Ala	Val	Gly	Met	Asp	Gly	Leu	Glu	Lys	His	Arg
545					550					555					560
Leu	Val	Ser	Arg	Thr	His	Ser	Ser	Pro	Ala	Ala	Ser	Val	Leu	Pro	His
				565					570					575	
Pro	Ala	Met	Asp	Arg	Pro	Leu	Gln	Pro	Gly	Ser	Ala	Thr	Gly	Ile	Ala
				580				585					590		
Tyr	Asp	Pro	Leu	Met	Leu	Lys	His	Gln	Cys	Val	Cys	Gly	Asn	Ser	Thr
				595			600					605			
Thr	His	Pro	Glu	His	Ala	Gly	Arg	Ile	Gln	Ser	Ile	Trp	Ser	Arg	Leu
				610			615					620			

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Gln Glu Thr Gly Leu Leu Asn Lys Cys Glu Arg Ile Gln Gly Arg Lys
 625 630 635 640
 Ala Ser Leu Glu Glu Ile Gln Leu Val His Ser Glu His His Ser Leu
 645 650 655
 Leu Tyr Gly Thr Asn Pro Leu Asp Gly Gln Lys Leu Asp Pro Arg Ile
 660 665 670
 Leu Leu Gly Asp Asp Ser Gln Lys Phe Phe Ser Ser Leu Pro Cys Gly
 675 680 685
 Gly Leu Gly Val Asp Ser Asp Thr Ile Trp Asn Glu Leu His Ser Ser
 690 695 700
 Gly Ala Ala Arg Met Ala Val Gly Cys Val Ile Glu Leu Ala Ser Lys
 705 710 715 720
 Val Ala Ser Gly Glu Leu Lys Asn Gly Phe Ala Val Val Arg Pro Pro
 725 730 735
 Gly His His Ala Glu Glu Ser Thr Ala Met Gly Phe Cys Phe Phe Asn
 740 745 750
 Ser Val Ala Ile Thr Ala Lys Tyr Leu Arg Asp Gln Leu Asn Ile Ser
 755 760 765
 Lys Ile Leu Ile Val Asp Leu Asp Val His His Gly Asn Gly Thr Gln
 770 775 780
 Gln Ala Phe Tyr Ala Asp Pro Ser Ile Leu Tyr Ile Ser Leu His Arg
 785 790 795 800
 Tyr Asp Glu Gly Asn Phe Phe Pro Gly Ser Gly Ala Pro Asn Glu Val
 805 810 815
 Arg Phe Ile Ser Leu Glu Pro His Phe Tyr Leu Tyr Leu Ser Gly Asn
 820 825 830
 Cys Ile Ala
 835

<210> 9

<211> 1791

<212> DNA

<213> Homo sapiens

<400> 9

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 ggacgagagc agctcttggc tcagcaaaga atgcacagta tgatcagctc agtggatgtg 180
 aagtcagaag ttctgtggg cctggagccc atctcacctt tagacctaaag gacagacctc 240
 aggatgatga tgcccggtgt ggaccctgtt gtccgtgaga agcaattgca gcaggaatta 300
 cttcttatcc agcagcagca acaaatccag aagcagcttc tgatagcaga gtttcagaaa 360
 cagcatgaga acttgacacg gcagcaccag gctcagcttc aggagcatat caaggaactt 420
 ctagccataa aacagcaaca agaactccta gaaaaggagc agaaactgga gcagcagagg 480
 caagaacagg aagtagagag gcatcgagca gaacagcagc ttctctctct cagaggcaaa 540
 gatagaggac gagaaagggc agtggcaagt acagaagtaa agcagaagct tcaagagttc 600
 ctactgagta aatcagcaac gaaagacact ccaactaatg gaaaaaatca ttccgtgagc 660
 cgccatccca agctctggta cacggctgcc caccacacat cattggatca aagctctcca 720
 ccccttagtg gaacatctcc atcctacaag tacacattac caggagcaca agatgcaaaag 780
 gatgatttcc ccttcgaaa aactgaatcc tcagtcagta gcagttctcc aggtctgtgt 840
 cccagttcac caaacaatgg gccaaactgga agtggttactg aaaatgagac ttcggttttg 900
 cccctaccc ctcatgccga gcaaatggtt tcacagcaac gcatttctaatt tcatgaagat 960
 tccatgaacc tgctaagtct ttatacctct ccttcttttg ccaacattac cttggggctt 1020
 cccgcagtgc catcccagct caatgcttcg aattcactca aagaaaagca gaagtgtgag 1080
 acgcagacgc ttaggcaagg tggttcctctg cctgggcagt atggaggcag catcccggca 1140
 tcttcagacc accctcatgt tacttttagag ggaaagccac ccaacagcag ccaccaggct 1200
 ctctgcagc atttattatt gaaagaacaa atgcgacagc aaaagcttct tgtagctggt 1260
 ggagttccct tacatcctca gtctcccttg gcaacaaaag agagaatttc acctggcatt 1320
 agaggtaccc acaaattgcc ccgtcacaga cccctgaacc gaaccagtc tgcacctttg 1380
 cctcagagca cgttggctca gctggtcatt caacagcaac accagcaatt cttggagaag 1440
 cagaagcaat accagcagca gatccacatg aacaaactgc ttctgaaatc tattgaacaa 1500
 ctgaagcaac caggcagtca ccttgaggaa gcagaggaag agcttcaggg ggaccaggcg 1560

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atgcaggaag acagagcgcc ctctagtggc aacagcacta ggagcgacag cagtgtttgt 1620
 gtggatgaca cactgggaca agttggggct gtgaagggtca aggaggaacc agtggacagt 1680
 gatgaagatg ctcagatcca ggaaatggaa tctgggggagc aggtgtgttt tatgcaacag 1740
 gtaataggca aagatttagc tccaggattt gtaattaaag tcattatctg a 1791

<210> 10

<211> 546

<212> PRT

<213> Homo sapiens

<400> 10

Met His Ser Met Ile Ser Ser Val Asp Val Lys Ser Glu Val Pro Val
 1 5 10 15
 Gly Leu Glu Pro Ile Ser Pro Leu Asp Leu Arg Thr Asp Leu Arg Met
 20 25 30
 Met Met Pro Val Val Asp Pro Val Val Arg Glu Lys Gln Leu Gln Gln
 35 40 45
 Glu Leu Leu Leu Ile Gln Gln Gln Gln Ile Gln Lys Gln Leu Leu
 50 55 60
 Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
 65 70 75 80
 Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
 85 90 95
 Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
 100 105 110
 Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
 115 120 125
 Gly Lys Asp Arg Gly Arg Glu Arg Ala Val Ala Ser Thr Glu Val Lys
 130 135 140
 Gln Lys Leu Gln Glu Phe Leu Leu Ser Lys Ser Ala Thr Lys Asp Thr
 145 150 155 160
 Pro Thr Asn Gly Lys Asn His Ser Val Ser Arg His Pro Lys Leu Trp
 165 170 175
 Tyr Thr Ala Ala His His Thr Ser Leu Asp Gln Ser Ser Pro Pro Leu
 180 185 190
 Ser Gly Thr Ser Pro Ser Tyr Lys Tyr Thr Leu Pro Gly Ala Gln Asp
 195 200 205
 Ala Lys Asp Asp Phe Pro Leu Arg Lys Thr Glu Ser Ser Val Ser Ser
 210 215 220
 Ser Ser Pro Gly Ser Gly Pro Ser Ser Pro Asn Asn Gly Pro Thr Gly
 225 230 235 240
 Ser Val Thr Glu Asn Glu Thr Ser Val Leu Pro Pro Thr Pro His Ala
 245 250 255
 Glu Gln Met Val Ser Gln Gln Arg Ile Leu Ile His Glu Asp Ser Met
 260 265 270
 Asn Leu Leu Ser Leu Tyr Thr Ser Pro Ser Leu Pro Asn Ile Thr Leu
 275 280 285
 Gly Leu Pro Ala Val Pro Ser Gln Leu Asn Ala Ser Asn Ser Leu Lys
 290 295 300
 Glu Lys Gln Lys Cys Glu Thr Gln Thr Leu Arg Gln Gly Val Pro Leu
 305 310 315 320
 Pro Gly Gln Tyr Gly Gly Ser Ile Pro Ala Ser Ser Ser His Pro His
 325 330 335
 Val Thr Leu Glu Gly Lys Pro Pro Asn Ser Ser His Gln Ala Leu Leu
 340 345 350
 Gln His Leu Leu Leu Lys Glu Gln Met Arg Gln Gln Lys Leu Leu Val
 355 360 365
 Ala Gly Gly Val Pro Leu His Pro Gln Ser Pro Leu Ala Thr Lys Glu
 370 375 380
 Arg Ile Ser Pro Gly Ile Arg Gly Thr His Lys Leu Pro Arg His Arg
 385 390 395 400
 Pro Leu Asn Arg Thr Gln Ser Ala Pro Leu Pro Gln Ser Thr Leu Ala

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          405          410          415
Gln Leu Val Ile Gln Gln Gln His Gln Gln Phe Leu Glu Lys Gln Lys
          420          425          430
Gln Tyr Gln Gln Gln Ile His Met Asn Lys Leu Leu Ser Lys Ser Ile
          435          440          445
Glu Gln Leu Lys Gln Pro Gly Ser His Leu Glu Glu Ala Glu Glu Glu
          450          455          460
Leu Gln Gly Asp Gln Ala Met Gln Glu Asp Arg Ala Pro Ser Ser Gly
465          470          475          480
Asn Ser Thr Arg Ser Asp Ser Ser Ala Cys Val Asp Asp Thr Leu Gly
          485          490          495
Gln Val Gly Ala Val Lys Val Lys Glu Glu Pro Val Asp Ser Asp Glu
          500          505          510
Asp Ala Gln Ile Gln Glu Met Glu Ser Gly Glu Gln Ala Ala Phe Met
          515          520          525
Gln Gln Val Ile Gly Lys Asp Leu Ala Pro Gly Phe Val Ile Lys Val
          530          535          540
Ile Ile
545

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<210> 11

<211> 590

<212> PRT

<213> Homo sapiens

<400> 11

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Met His Ser Met Ile Ser Ser Val Asp Val Lys Ser Glu Val Pro Val
1          5          10          15
Gly Leu Glu Pro Ile Ser Pro Leu Asp Leu Arg Thr Asp Leu Arg Met
          20          25          30
Met Met Pro Val Val Asp Pro Val Val Arg Glu Lys Gln Leu Gln Gln
          35          40          45
Glu Leu Leu Leu Ile Gln Gln Gln Gln Ile Gln Lys Gln Leu Leu
          50          55          60
Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
65          70          75          80
Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
          85          90          95
Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
          100          105          110
Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
          115          120          125
Gly Lys Asp Arg Gly Arg Glu Arg Ala Val Ala Ser Thr Glu Val Lys
          130          135          140
Gln Lys Leu Gln Glu Phe Leu Leu Ser Lys Ser Ala Thr Lys Asp Thr
145          150          155          160
Pro Thr Asn Gly Lys Asn His Ser Val Ser Arg His Pro Lys Leu Trp
          165          170          175
Tyr Thr Ala Ala His His Thr Ser Leu Asp Gln Ser Ser Pro Pro Leu
          180          185          190
Ser Gly Thr Ser Pro Ser Tyr Lys Tyr Thr Leu Pro Gly Ala Gln Asp
          195          200          205
Ala Lys Asp Asp Phe Pro Leu Arg Lys Thr Ala Ser Glu Pro Asn Leu
          210          215          220
Lys Val Arg Ser Arg Leu Lys Gln Lys Val Ala Glu Arg Arg Ser Ser
225          230          235          240
Pro Leu Leu Arg Arg Lys Asp Gly Asn Val Val Thr Ser Phe Lys Lys
          245          250          255
Arg Met Phe Glu Val Thr Glu Ser Ser Val Ser Ser Ser Pro Gly
          260          265          270
Ser Gly Pro Ser Ser Pro Asn Asn Gly Pro Thr Gly Ser Val Thr Glu

```

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275	280	285
Asn Glu Thr Ser Val Leu Pro Pro Thr Pro His Ala Glu Gln Met Val		
290	295	300
Ser Gln Gln Arg Ile Leu Ile His Glu Asp Ser Met Asn Leu Leu Ser		
305	310	315
Leu Tyr Thr Ser Pro Ser Leu Pro Asn Ile Thr Leu Gly Leu Pro Ala		
	325	330
		335
Val Pro Ser Gln Leu Asn Ala Ser Asn Ser Leu Lys Glu Lys Gln Lys		
	340	345
		350
Cys Glu Thr Gln Thr Leu Arg Gln Gly Val Pro Leu Pro Gly Gln Tyr		
	355	360
		365
Gly Gly Ser Ile Pro Ala Ser Ser Ser His Pro His Val Thr Leu Glu		
	370	375
		380
Gly Lys Pro Pro Asn Ser Ser His Gln Ala Leu Leu Gln His Leu Leu		
385	390	395
Leu Lys Glu Gln Met Arg Gln Gln Lys Leu Leu Val Ala Gly Gly Val		
	405	410
		415
Pro Leu His Pro Gln Ser Pro Leu Ala Thr Lys Glu Arg Ile Ser Pro		
	420	425
		430
Gly Ile Arg Gly Thr His Lys Leu Pro Arg His Arg Pro Leu Asn Arg		
	435	440
		445
Thr Gln Ser Ala Pro Leu Pro Gln Ser Thr Leu Ala Gln Leu Val Ile		
	450	455
		460
Gln Gln Gln His Gln Gln Phe Leu Glu Lys Gln Lys Gln Tyr Gln Gln		
465	470	475
Gln Ile His Met Asn Lys Leu Leu Ser Lys Ser Ile Glu Gln Leu Lys		
	485	490
		495
Gln Pro Gly Ser His Leu Glu Glu Ala Glu Glu Glu Leu Gln Gly Asp		
	500	505
		510
Gln Ala Met Gln Glu Asp Arg Ala Pro Ser Ser Gly Asn Ser Thr Arg		
	515	520
		525
Ser Asp Ser Ser Ala Cys Val Asp Asp Thr Leu Gly Gln Val Gly Ala		
	530	535
		540
Val Lys Val Lys Glu Glu Pro Val Asp Ser Asp Glu Asp Ala Gln Ile		
545	550	555
Gln Glu Met Glu Ser Gly Glu Gln Ala Ala Phe Met Gln Gln Val Ile		
	565	570
		575
Gly Lys Asp Leu Ala Pro Gly Phe Val Ile Lys Val Ile Ile		
	580	585
		590

<210> 12

<211> 1084

<212> PRT

<213> Homo sapiens

<400> 12

Met Ser Ser Gln Ser His Pro Asp Gly Leu Ser Gly Arg Asp Gln Pro	
1	5
Val Glu Leu Leu Asn Pro Ala Arg Val Asn His Met Pro Ser Thr Val	
	20
	25
Asp Val Ala Thr Ala Leu Pro Leu Gln Val Ala Pro Ser Ala Val Pro	
	35
	40
Met Asp Leu Arg Leu Asp His Gln Phe Ser Leu Pro Val Ala Glu Pro	
	50
	55
Ala Leu Arg Glu Gln Gln Leu Gln Gln Glu Leu Leu Ala Leu Lys Gln	
65	70
	75
Lys Gln Gln Ile Gln Arg Gln Ile Leu Ile Ala Glu Phe Gln Arg Gln	
	85
	90
His Glu Gln Leu Ser Arg Gln His Glu Ala Gln Leu His Glu His Ile	
	100
	105
Lys Gln Gln Gln Glu Met Leu Ala Met Lys His Gln Gln Glu Leu Leu	
	110

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115					120					125					
Glu	His	Gln	Arg	Lys	Leu	Glu	Arg	His	Arg	Gln	Glu	Gln	Glu	Leu	Glu
130						135					140				
Lys	Gln	His	Arg	Glu	Gln	Lys	Leu	Gln	Gln	Leu	Lys	Asn	Lys	Glu	Lys
145					150					155					160
Gly	Lys	Glu	Ser	Ala	Val	Ala	Ser	Thr	Glu	Val	Lys	Met	Lys	Leu	Gln
				165					170						175
Glu	Phe	Val	Leu	Asn	Lys	Lys	Lys	Ala	Leu	Ala	His	Arg	Asn	Leu	Asn
			180					185					190		
His	Cys	Ile	Ser	Ser	Asp	Pro	Arg	Tyr	Trp	Tyr	Gly	Lys	Thr	Gln	His
		195				200					205				
Ser	Ser	Leu	Asp	Gln	Ser	Ser	Pro	Pro	Gln	Ser	Gly	Val	Ser	Thr	Ser
		210				215					220				
Tyr	Asn	His	Pro	Val	Leu	Gly	Met	Tyr	Asp	Ala	Lys	Asp	Asp	Phe	Pro
225					230					235					240
Leu	Arg	Lys	Thr	Ala	Ser	Glu	Pro	Asn	Leu	Lys	Leu	Arg	Ser	Arg	Leu
				245					250						255
Lys	Gln	Lys	Val	Ala	Glu	Arg	Arg	Ser	Ser	Pro	Leu	Leu	Arg	Arg	Lys
			260					265					270		
Asp	Gly	Pro	Val	Val	Thr	Ala	Leu	Lys	Lys	Arg	Pro	Leu	Asp	Val	Thr
		275					280					285			
Asp	Ser	Ala	Cys	Ser	Ser	Ala	Pro	Gly	Ser	Gly	Pro	Ser	Ser	Pro	Asn
		290				295					300				
Asn	Ser	Ser	Gly	Ser	Val	Ser	Ala	Glu	Asn	Gly	Ile	Ala	Pro	Ala	Val
305					310					315					320
Pro	Ser	Ile	Pro	Ala	Glu	Thr	Ser	Leu	Ala	His	Arg	Leu	Val	Ala	Arg
				325					330						335
Glu	Gly	Ser	Ala	Ala	Pro	Leu	Pro	Leu	Tyr	Thr	Ser	Pro	Ser	Leu	Pro
			340					345				350			
Asn	Ile	Thr	Leu	Gly	Leu	Pro	Ala	Thr	Gly	Pro	Ser	Ala	Gly	Thr	Ala
		355					360					365			
Gly	Gln	Gln	Asp	Thr	Glu	Arg	Leu	Thr	Leu	Pro	Ala	Leu	Gln	Gln	Arg
		370				375					380				
Leu	Ser	Leu	Phe	Pro	Gly	Thr	His	Leu	Thr	Pro	Tyr	Leu	Ser	Thr	Ser
385					390					395					400
Pro	Leu	Glu	Arg	Asp	Gly	Gly	Ala	Ala	His	Ser	Pro	Leu	Leu	Gln	His
				405					410						415
Met	Val	Leu	Leu	Glu	Gln	Pro	Pro	Ala	Gln	Ala	Pro	Leu	Val	Thr	Gly
				420				425					430		
Leu	Gly	Ala	Leu	Pro	Leu	His	Ala	Gln	Ser	Leu	Val	Gly	Ala	Asp	Arg
		435					440					445			
Val	Ser	Pro	Ser	Ile	His	Lys	Leu	Arg	Gln	His	Arg	Pro	Leu	Gly	Arg
		450				455					460				
Thr	Gln	Ser	Ala	Pro	Leu	Pro	Gln	Asn	Ala	Gln	Ala	Leu	Gln	His	Leu
465					470					475					480
Val	Ile	Gln	Gln	Gln	His	Gln	Gln	Phe	Leu	Glu	Lys	His	Lys	Gln	Gln
				485				490							495
Phe	Gln	Gln	Gln	Gln	Leu	Gln	Met	Asn	Lys	Ile	Ile	Pro	Lys	Pro	Ser
				500				505				510			
Glu	Pro	Ala	Arg	Gln	Pro	Glu	Ser	His	Pro	Glu	Glu	Thr	Glu	Glu	Glu
		515				520					525				
Leu	Arg	Glu	His	Gln	Ala	Leu	Leu	Asp	Glu	Pro	Tyr	Leu	Asp	Arg	Leu
		530				535					540				
Pro	Gly	Gln	Lys	Glu	Ala	His	Ala	Gln	Ala	Gly	Val	Gln	Val	Lys	Gln
545					550					555					560
Glu	Pro	Ile	Glu	Ser	Asp	Glu	Glu	Glu	Ala	Glu	Pro	Pro	Arg	Glu	Val
				565					570						575
Glu	Pro	Gly	Gln	Arg	Gln	Pro	Ser	Glu	Gln	Glu	Leu	Leu	Phe	Arg	Gln
				580				585					590		
Gln	Ala	Leu	Leu	Leu	Glu	Gln	Gln	Arg	Ile	His	Gln	Leu	Arg	Asn	Tyr
		595				600					605				
Gln	Ala	Ser	Met	Glu	Ala	Ala	Gly	Ile	Pro	Val	Ser	Phe	Gly	Gly	His

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610	615	620
Arg Pro Leu Ser Arg	Ala Gln Ser Ser Pro	Ala Ser Ala Thr Phe Pro
625	630	635
Val Ser Val Gln Glu Pro	Pro Thr Lys Pro Arg	Phe Thr Thr Gly Leu
645	650	655
Val Tyr Asp Thr Leu Met	Leu Lys His Gln Cys	Thr Cys Gly Ser Ser
660	665	670
Ser Ser His Pro Glu His	Ala Gly Arg Ile Gln	Ser Ile Trp Ser Arg
675	680	685
Leu Gln Glu Thr Gly Leu	Arg Gly Lys Cys Glu	Cys Ile Arg Gly Arg
690	695	700
Lys Ala Thr Leu Glu Glu	Leu Gln Thr Val His	Ser Glu Ala His Thr
705	710	715
Leu Leu Tyr Gly Thr Asn	Pro Leu Asn Arg Gln	Lys Leu Asp Ser Lys
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24/25

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



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WO 02/102984 A3

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- (21) International Application Number: PCT/US02/19051
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60/316,995 4 September 2001 (04.09.2001) US
- (71) Applicant (for all designated States except US):
SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH [US/US]; 1275 York Avenue, New York, NY 10021 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **RICHON, Victoria** [US/US]; 160 Theodore Fremd Street, #A11, Rye, NY 10580 (US). **ZHOU, Xianbo** [CN/US]; 43 Bradley Street, Dobbs Ferry, NY 10522 (US). **RIFKIND, Richard, A.** [US/US]; 425 East 58th Street, #48A, New York, NY 10022 (US). **MARKS, Paul, A.** [US/US]; 7 Rossiter Road, Washington, CT 06793 (US).
- (74) Agents: **BROOK, David, E.** et al.; Hamilton, Brook, Smith & Reynolds, P.C., 530 Virginia Road, P.O. Box 9133, Concord, MA 01742-9133 (US).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
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13 November 2003
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/102984 A3

(54) Title: HDAC9 POLYPEPTIDES AND POLYNUCLEOTIDES AND USES THEREOF

(57) Abstract: The present invention features substantially pure HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), an HDRP(Δ NLS) polypeptides, and isolated nucleic acid molecules encoding those polypeptides. The present invention also features vectors containing HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), and HDRP(Δ NLS) nucleic acid sequences, and cells containing those vectors.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/19051-

A. CLASSIFICATION OF SUBJECT MATTER IPC(7) : C12N 9/78, 9/00, 9/14, 1/20, 15/00; C07H 21/04 US CL : 435/227, 183, 195, 252.3, 320.1; 536/23.2 According to International Patent Classification (IPC) or to both national classification and IPC																				
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 435/227, 183, 195, 252.3, 320.1; 536/23.2 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) STN AND WEST. Sequence search in Swissprot, EST, N-GeneSeq, PIR_71, SPTREMBL & issued US patents.																				
C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1"> <thead> <tr> <th>Category *</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X</td> <td>NAGASE et al. Prediction of Coding Sequences of Unidentified Human Genes. XI. The Complete Sequences of 100 New cDNA Clones from Brain Which Code for Large Proteins in Vitro. DNA Research November 1998, Vol 5, pages 277-286. See Table 1, Accession No. AB018287 is 58.8% similar to DNA sequence of SEQ ID NO : 1, claim 4 (g).</td> <td>4</td> </tr> <tr> <td>A, P</td> <td>ZHOU et al. Cloning and Characterization of a histone deacetylase, HDAC9. PNAS, 11 September 2001, Vol. 98, No. 19, pages 10572-10577.</td> <td>1-9, 29</td> </tr> <tr> <td>A</td> <td>WANG et al. HDAC4, a Human Histone Deacetylase Related to Yeast HDA1, Is a Transcriptional Corepressor. Molecular and Cellular Biology, November 1999, Vol. 19, No. 11, pages 7816-7827.</td> <td>1-9, 29</td> </tr> </tbody> </table>			Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X	NAGASE et al. Prediction of Coding Sequences of Unidentified Human Genes. XI. The Complete Sequences of 100 New cDNA Clones from Brain Which Code for Large Proteins in Vitro. DNA Research November 1998, Vol 5, pages 277-286. See Table 1, Accession No. AB018287 is 58.8% similar to DNA sequence of SEQ ID NO : 1, claim 4 (g).	4	A, P	ZHOU et al. Cloning and Characterization of a histone deacetylase, HDAC9. PNAS, 11 September 2001, Vol. 98, No. 19, pages 10572-10577.	1-9, 29	A	WANG et al. HDAC4, a Human Histone Deacetylase Related to Yeast HDA1, Is a Transcriptional Corepressor. Molecular and Cellular Biology, November 1999, Vol. 19, No. 11, pages 7816-7827.	1-9, 29						
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<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.																				
<table border="1"> <thead> <tr> <th colspan="2">Special categories of cited documents:</th> <th></th> </tr> </thead> <tbody> <tr> <td>* "A"</td> <td>document defining the general state of the art which is not considered to be of particular relevance</td> <td>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</td> </tr> <tr> <td>* "B"</td> <td>earlier application or patent published on or after the international filing date</td> <td>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</td> </tr> <tr> <td>* "L"</td> <td>document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</td> <td>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</td> </tr> <tr> <td>* "O"</td> <td>document referring to an oral disclosure, use, exhibition or other means</td> <td>"&" document member of the same patent family</td> </tr> <tr> <td>* "P"</td> <td>document published prior to the international filing date but later than the priority date claimed</td> <td></td> </tr> </tbody> </table>			Special categories of cited documents:			* "A"	document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	* "B"	earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	* "L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	* "O"	document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	* "P"	document published prior to the international filing date but later than the priority date claimed	
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* "B"	earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone																		
* "L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art																		
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* "P"	document published prior to the international filing date but later than the priority date claimed																			
Date of the actual completion of the international search 30 October 2002 (30.10.2002)		Date of mailing of the international search report 13 MAR 2003																		
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230		Authorized officer Tekchand Saidha Telephone No. (703) 308-0196																		

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/190 51

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-9 & 29 (SEQ ID NOS : 1 & 2)

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/19051

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-9, 29, drawn to isolated nucleic acid, the encoded protein and protein composition.

Group II, claim(s) 10, drawn to antibody.

Group III, claim(s) 11-13, drawn to a method of identifying a compound - modulate DNA expression.

Group IV, claim(s) 14-19, 33, drawn to a method of identifying a compound that modulate enzymatic activity.

Group V, claim(s) 20-25, 34, drawn to a method of identifying a compound that modulate transcriptional repression activity of the polypeptide.

Group VI, claim(s) 26-27, drawn to a method of identifying a compound that modulate expression of a nucleic acid molecule.

Group VII, claim(s) 28, drawn to a method of identifying a polypeptide that interacts with a polypeptide of claim 1 in a two-hybrid system.

Group VIII, claim(s) 30-32, drawn to a method of diagnosing a cell proliferation disease.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

1. SEQ ID NO : 1 and 2 [HDAC9].
2. SEQ ID NO : 3 and 4 [HDAC9a].
3. SEQ ID NO : 5 and 6 [HDAC9- Δ NLS].
4. SEQ ID NO : 7 and 8 [HDAC9a- Δ NLS].
5. SEQ ID NO : 9 and 10 [HDRP- Δ NLS].

The claims are deemed to correspond to the species listed above in the following manner:

Each of the claims listed in groups I-VIII correspond to each of the 5 species which are structurally distinct.

The following claim(s) are generic: 1-5.

The inventions listed as Groups I-VIII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Group I has a special technical feature of the nucleotide sequence encoding a specific histone deacetylase which Groups II-VIII do not share; Group II has a special technical feature of the antibody to a specific histone deacetylase which Groups I & III-VIII do not share; Groups III-VIII employ nucleic acid or polypeptide in various method of identifying compounds or polypeptides for distinct uses. Further, in view of 37 CFR 1.475 (b), when claims corresponding to different categories of inventions are present then only (3) applies and additional methods of use are deemed to lack unity.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: The various species correspond to nucleic acid and polypeptide sequences which are structurally and in activity distinct from each other, therefore lack the same or corresponding special technical feature.